



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Environmental Regulation of Advanced Innovative Biotechnologies

Citation for published version:

Tait, E 2016, *Environmental Regulation of Advanced Innovative Biotechnologies: Anticipating future regulatory oversight. Report to ShARE Group of Environment Agencies of the UK and Republic of Ireland.* . Innogen Institute Report, Edinburgh. <<https://www.sepa.org.uk/media/219333/environmental-regulation-of-advanced-innovative-biotechnologies-anticipating-future-regulatory-oversight.pdf>>

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.





SHARE PROJECT #97

**ENVIRONMENTAL REGULATION OF ADVANCED INNOVATIVE BIOTECHNOLOGIES:
ANTICIPATING FUTURE REGULATORY OVERSIGHT**

JOYCE TAIT

Innogen Institute,
University of Edinburgh,
Old Surgeons Hall,
High School Yards,
Edinburgh EH1 1LZ
www.innogen.ac.uk

26th April, 2016

Contents

<i>Acronym List</i>	3
<i>Abstract</i>	4
<i>Definitions used in Report</i>	5
<i>Executive Summary</i>	6
<i>1. Why should the ShARE group of EAs be interested in AIBs? - The governance concept and its relationship to regulation</i>	7
<i>2. Why should the ShARE group of EAs be interested in AIBs? - The potential contribution of AIBs to the bioeconomy.</i>	9
2.1 Potential disruptive and incremental impacts of AIBs.....	9
2.2 Scale and impact of synthetic biology related developments	12
2.3 Innovation policy support for synthetic biology	15
2.4 Future prospects for AIBs	16
<i>3 Regulation and governance of GMOs and future AIBs</i>	17
3.1 Potential environmental benefits of AIBs	17
3.2 Potential environmental hazards of AIBs.....	18
3.3 The role of the precautionary principle (PP) in the governance of AIBs in the EU.	20
3.4 Stakeholder engagement and public attitudes to GMOs and AIBs.....	21
3.5 Current regulatory systems for GMOs	25
3.5.1 Contained use	25
3.5.2 Deliberate release	26
3.5.3 EU opt-out legislation	27
3.5.4 International differences in regulatory systems for GMOs.....	27
3.6 Critique of the current European regulatory system for GMOs.	28
<i>4. Future governance of AIBs</i>	31
4.1 Future governance of AIBs in the EU	31
4.2 Future UN governance of AIBs.....	33
4.3 The special case of gene editing	34
4.4 Issues arising from gene drive technologies	35
<i>5. Conclusions and recommendations: a proportionate and adaptive approach to the governance of AIBs</i>	36
5.1 The potential impacts of AIB-related innovation.....	37
5.2 Supporting decision making on proportionate and adaptive regulation of AIBs.....	38
5.3 Constructive stakeholder engagement.....	40
5.4 Combining proportionate, adaptive governance and constructive stakeholder engagement	42
5.4.1 The potential of a Framework Standard	43
5.5 Recommendations: potential roles for the EAs in future governance of AIBs	45
<i>References</i>	46

Acronym List

ACRE – Advisory Committee on Releases to the Environment
AIBs – Advanced Innovative Biotechnologies
ATLC – Agri-Tech Leadership Council
BBSRC – Biotechnology and Biological Sciences Research Council
BSI – British Standards Institution
CA – UK Competent Authority
CAP – Common Agricultural Policy
CBD – UN Convention on Biological Diversity
CRISPR – Clustered Regularly-Interspaced Short Palindromic Repeats
CRISPR-Cas9 – CRISPR system delivering the CAS9 protein
CST – Council for Science and Technology
DEFRA – Department for Environment, Food and Rural Affairs
DNA – Deoxyribonucleic Acid
EAs – Environment Agencies (consortium of UK and Irish environment agencies comprising the Scottish Environment Protection Agency; Natural Resources Wales; the Environment Agency; Northern Ireland Environment Agency; and the Environmental Protection Agency Ireland)
EASAC – European Academies Science Advisory Council
EFSA – European Food Safety Authority
EPA – Environmental Protection Agency (Ireland)
EU – European Union
FSA – Food Standards Agency (UK)
GM – Genetic Modification
GMOs – Genetically Modified Organisms
GMO(CU) – Genetically Modified Organisms (Contained Use)
GMP – Good Manufacturing Practice
GVA – Gross Value Added
HoC – UK House of Commons
HSE – UK Health and Safety Executive
HSENI – Health and Safety Executive for Northern Ireland
IBioIC – Industrial Biotechnology Innovation Centre
IBLF – Industrial Biotechnology Leadership Forum
ICT – Information and Communication Technologies
NGOs – Non-Governmental Organisations
OECD – Organisation for Economic Cooperation and Development
PP – Precautionary Principle
R&D – Research and Development
ROI – Republic of Ireland
SACGM – Scientific Advisory Committee on Genetic Modification
SASA – Science and Advice for Scottish Agriculture
SBLC – UK Synthetic Biology Leadership Council
SEPA – Scottish Environment Protection Agency
ShARE – Shared Agencies Regulatory Evidence (Programme)
TALEN – Transcription Activator-Like Effector-based Nuclease
UK – United Kingdom
UN – United Nations
US – United States
ZFN – Zinc Finger Nuclease

Abstract

Advanced Innovative Biotechnologies (AIBs, see Box. 1 for definitions) are an emerging sector of increasing scientific and public policy interest. The sector offers the potential to deliver on the shared purpose of the UK and Republic of Ireland environmental authorities to protect and improve the environment, to protect public health and to support sustainable economic growth. Beyond the expected benefits it is also important to consider whether there are any potential hazards or environmental threats from these innovations that would not be captured by regulations currently in place. The technology is at an early but rapidly developing stage, therefore it is timely to assess the scale and likely impact of the AIB sector in the near to distant future, as well as considering if the sector might present unique risks that are unconsidered by present regulatory approaches and what are these risk likely to be.

To this end, a ShARE¹ Programme was developed to engage a recognised expert to examine the opportunities and threats posed by the AIB sector as it develops. The purpose of the report is to drive forward a deliberative discourse on how the EAs could contribute in future to a more proportionate and adaptive governance system that would enable AIBs to deliver their full potential to the bioeconomy and the circular economy, and also to the improvement of the natural environment. This report constitutes the output of this programme stream.

¹ The ShARE (Shared Agencies Regulatory Evidence) Programme is run by a consortium of UK and Irish environment agencies: the Scottish Environment Protection Agency; Natural Resources Wales; the Environment Agency; Northern Ireland Environment Agency; and the Environmental Protection Agency Ireland

Advanced Innovative Biotechnologies



Why do we need definitions?

For AIBs in early stages of development, the pressure to formalise an agreed definition is related to the desire to reach an early decision on the appropriate regulatory system, i.e. the new development is defined in a way that will ensure its capture by a particular regulatory system already in existence. For most AIBs, the choice of regulatory precedent is likely to be that in place for GMOs, potentially with some technology-specific adaptations.

Synthetic biology

The currently agreed EU definition is "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms." (i)

The UK Synthetic Biology Roadmap describes it as "the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems [with] the potential to deliver important new applications and improve existing industrial processes – resulting in economic growth and job creation" (ii)

Gene synthesis

Gene synthesis is treated here as part of the synthetic biology family of techniques. It is used to produce synthetic biological circuits, stretches of DNA manipulated to change gene expression within cells and cause the cell to produce a desired product. Rapid developments in gene synthesis, from the de novo synthesis of existing complex gene sequences to the creation of novel bacterial plasmids that have not previously existed in nature (artificial gene synthesis), along with major reductions in the costs of synthesis, are opening up new possibilities for the large scale manufacture of complex molecules

Gene editing

Gene Editing, is a process in which DNA is inserted, deleted or replaced in the genome of an organism using engineered nucleases, or "molecular scissors", resulting in targeted mutations ('edits'). (The process also occurs naturally.) Techniques used include zinc finger nucleases (ZFNs), transcription activator-like effector-based nucleases (TALENs), and the CRISPR system (clustered regularly-interspaced short palindromic repeats). CRISPR– Cas9 (delivering the CAS9 protein) is being used, among other things, to aid understanding of epigenetic processes.

Gene Drives

Also based on the CRISPR-CAS9 system, a gene drive is designed to actively copy a gene drive modification on one chromosome to its partner chromosome, providing a process of inheritance whereby a gene is guaranteed to pass from one generation to the next, and ultimately throughout a population. It has been proposed as a technique for changing wild populations of harmful organisms such as mosquitoes to be less dangerous, or to wipe out such populations, or to control invasive species

(i) EU Scientific Committee's. *Opinion on Synthetic Biology I : Definition* (2014)

(ii) UK Synthetic Biology Roadmap Coordination Group. *A synthetic biology roadmap for the UK* (2012)

Executive Summary



Purpose

This report has been commissioned with the objective of stimulating and guiding future discussions among the UK and Republic of Ireland (ROI) EPAs, as well as AIB-related practitioners and the wider public, as to how we can develop a proportionate and adaptive governance framework; one which can ensure the environment and public health are not compromised by any unique risks posed by AIBs, whilst supporting the delivery of the benefits AIBs are predicted to deliver for the UK economy, the environment and wider society.

Overview



This report assesses the scale and likely impact of AIBs on the ability of the UK and ROI to regulate the relevant sectors in future, concluding that innovations arising from AIBs are expected to be incremental, enabling step-wise improvements in innovation pathways, creating competitive advantage for the companies that adopt them.



Given the speed at which this sector is developing, this report goes on to consider the extent to which the AIB sector presents unique risks that are unconsidered by present regulatory approaches. The Health & Safety Executive conducted research to address this question in 2012 – the resulting report concluded that: “the current regulatory framework for GMOs in Britain adequately covers present and near future synthetic biology activities”



The report notes that the EU have indicated their intention that the regulatory systems to be applied to AIBs in the EU will be those currently in place for genetically modified organisms (GMOs), in contained use and for deliberate release. Given this, the role of the precautionary principle (PP) in the governance of AIBs in the EU is considered. The report concludes that the process based approach to risk assessment which underpins the PP, makes it too blunt an instrument in an era of novel technologies and materials which offer “smart solutions”



Recommendations

Given the limitations of the “better safe than sorry” ethos of the PP in supporting innovative AIBs, the report recommends the adoption of a new systemic approach for regulators and policy makers to think constructively about the governance of advanced innovative technologies.

This more adaptive risk governance approach for AIBs would aim to be:

- Enabling of innovation,
- Minimising risk to people and the environment
- Balancing the interests and values of all relevant stakeholders.

Conclusion



The UK and Eire Environment Agencies need to combine proportionate and adaptive governance of Advanced Innovative Biotechnologies (AIB's) with a constructive approach to stakeholder engagement.

This would provide for trade-offs between threats and opportunities and support smarter regulatory approaches that balance potential societal and economic benefits and potential risks, particularly where both are uncertain in the early stages of technology development

1. Why should the ShARE group of EAs be interested in AIBs? - The governance concept and its relationship to regulation

Generally speaking these agencies advise their relevant Governments and other constituencies about issues relating to the environment and its natural resources and also act in a regulatory capacity for the implementation of environmental regulation. EAs have a crucial role in implementing governance processes in the regulatory jurisdictions they serve and, given the broad range of different interpretations of the term 'governance', it is important to clarify how it is used in this report. Most definitions rest on three dimensions: authority, decision-making and accountability, determining who has power, who makes decisions, how other players make their voices heard and how account is rendered². In the context of EU policy making and regulation, from the 1980s the concept of governance began to acquire specific meanings arising from a range of pressures: the emergence of unexpected problems with technologies previously considered safe (e.g. organochlorine insecticides, nuclear power); a decline in public trust of government bodies and industry; the rapid pace of scientific development and technological change; the difficulties policymakers had in keeping up with this pace of change; commercial pressures arising from globalisation; and the role of internet-facilitated societal movements. Social science disciplines have played an important, but not always impartial, role in understanding these changes, focusing on issues of risk and innovation, questioning the authority of scientific expertise and the validity of scientific evidence used to support policy and regulatory decisions by government, and focusing on uncertainty and the precautionary principle (or approach) as the policy answer to these challenges (Tait, 2014).

Alongside this new "bottom-up" governance agenda, in technology-related areas there is still a need for regulation based on "top-down" command and control, backed up by sanctions and penalties to ensure the safety of innovative products and processes to human health and the environment. The term 'governance' as used here incorporates this European interpretation of the governance concept (including formal legislation, less formal policy initiatives and stakeholder concerns and issues) given that it has been so influential on the development of genetically modified organisms (GMOs) and more recently AIBs.

Section 3.4 focuses on stakeholder perceptions of AIBs, and notes how this specifically European governance agenda has supported the persistent impression of public opposition to AIBs that has not been adaptive to increasing evidence of the safety of deliberate release of GMOs. Section 5 introduces a new systemic approach for regulators and policy makers to think constructively about the governance of advanced innovative technologies in the context of AIBs and also more generally. It includes making governance more adaptive to the needs of industry sectors developing new technologies to meet societal needs, and more proportionate to potential hazards, while continuing to protect safety, quality and efficacy.

The ShARE group of EAs are charged with implementing the relevant EU Directives, as they have been translated into national or regional regulations, to protect the environment and contribute to sustainable economic growth. They are also expected to alert their Governments to potential emerging hazards that are not covered by existing regulatory systems, with an emphasis on basing decisions and representations on the best available scientific evidence.

Within the EU, as outlined in more detail in Section 3, the EAs face a major challenge in delivering on this remit. The GM regulatory system which is seen as the logical precedent for future

² Canadian Institute on Governance (<http://iog.ca/wp-content/uploads/2014/11/About-IOG.pdf>)

regulation of AIBs is widely regarded as 'unfit for purpose' in its present role (Baulcombe *et al.*, 2014; Tait, 2009c; UK Advisory Committee on Releases to the Environment (ACRE), 2013).

Challenges from these critics of the current EU regulatory system are based on:

- the extent of political influence on regulatory decision making, as opposed to scientific evidence related to risks and benefits;
- the fact that the EU regulatory system is process, rather than product-based: in the EU, unlike the systems in operation in most of the rest of the world, the regulatory focus is on the process by which a new innovation is derived (genetic modification) rather than on the properties of the final innovation itself (Tait, 2008);
- the focus on uncertainty rather than evidence (Tait, 2014) supported by the EU adherence to a strong interpretation of the precautionary principle (PP) which, from a legal perspective has proved extremely difficult to implement in practice (Sunstein, 2005), and has enabled strong social amplification of uncertainty in dealing with AIBs (Stirling, 2014).

Two decades of accumulating evidence, showing negligible environmental risks, and considerable environmental and economic benefits from the use of GM crops, has failed to expedite regulatory approvals for the growing of GM crops in the EU (Baulcombe *et al.*, 2014). Raybould and Poppy (2012), based on research by Evans *et al.* (2006), have suggested that the societal consensus needed for the definition of clear operational objectives for a regulatory system is lacking, preventing the delivery of decisions based on scientific evidence (International Risk Governance Council (IRGC), 2009).

Mittra *et al.* (2014) have suggested that new risk governance and regulatory approaches will be required if the EU is to retain a role in the development of AIBs with their attendant environmental and economic benefits in the 21st century. These new regulatory approaches will need to be better adapted to the opportunities presented by AIBs, and to be robust, flexible and democratic in the face of societal pressures while continuing to ensure safety for people and the environment.

If the EU regulatory system was better adapted to the properties, hazards and benefits of GM crops, as is the case for example in Canada (Mittra *et al.*, 2014), proposals to base the regulation of synthetic biology and other AIBs on the current GM regulatory system (Buhk, 2014) would be logical and unproblematic. However, the combination of:

- a strongly politically influenced regulatory system,
- a lack of societal consensus leading to poorly defined policy objectives,
- the residue of an active environmental advocacy community with ideologically-motivated objections to the use of AIBs,
- policy over-commitment to the precautionary principle alongside unwillingness to adapt existing regulatory systems to new circumstances, and uncertainty about the nature of future products and processes arising from AIBs, adds up to a challenging decision making environment for EAs.

There is now strong evidence of the safety, quality and efficacy of the current generation of GM products and processes, and based on this evidence and on the nature of current proposed developments using from AIBs³ there is no reason to expect new types or degrees of hazard to arise from these AIB-related developments on a 5-10 year timescale (Buhk, 2014). Well informed speculation, based on experience of similar technologies and plausible scenarios about future

³ The circumstances are different for **gene drives**, as will be discussed in Section 4.4.

hazards and benefits is likely to be the best available basis for decision making today about the future regulation of AIBs. This opens up the decision making processes to advocacy based on vested interests and/or deeply held values (see Section 3.4) and the challenge for EAs is to identify such advocacy where it exists and to be equitably sceptical in their response to it.

2. Why should the ShARE group of EAs be interested in AIBs? - *The potential contribution of AIBs to the bioeconomy.*

2.1 Potential disruptive and incremental impacts of AIBs

The term ‘disruptive innovation’ is becoming widely used and is beginning to lose its original more restricted interpretation. However, distinguished from its counterpart ‘incremental innovation’, it remains a very useful concept when considering AIBs, their economic and societal impacts, and how they can most effectively be governed. Box 2 summarises the characteristics of disruptive and incremental innovation and notes that an innovation can be disruptive for one industry sector but incremental for another, as illustrated in Box 3. With any new AIB, the implications for policy and regulatory developments and also for societal acceptance will depend on the extent to which the AIB is expected to have a disruptive or incremental impact on particular industry sectors and the location of that impact along the development pipeline (from R&D through manufacture to marketing (Table 1).

Box 2. Disruptive and Incremental Innovation (Tait, 2007)

Disruptive innovation (also described as path-breaking or radical):

- Steps outside existing paradigms leading to discontinuities in innovation pathways, to major shifts in product types and their place in the market, and potentially to the creation of new industry sectors or radical re-structuring of existing sectors.
- Cannot be accommodated within a company’s current business model. It needs new areas of R&D; new modes of production; new routes to new markets.

Incremental innovation (also described as path-dependent):

- Presents few serious challenges to the prevailing company business models and can be relatively easily accommodated within them.
- Enables stepwise improvements in a company’s current innovation system, creating competitive advantage within the same sector.

An innovation that is path-breaking for one industry sector can be path dependent for another (see Box 3).

Box 3. Example: GM crops as a disruptive innovation

Pesticide development was the established business model for the agrochemical industry when it first began to develop GM crops in the 1980s and GM crops were disruptive at all stages of the innovation process: R&D, manufacture and the market. However, the seed company sector at the time would have been equally well placed to develop this new technology, and while GM would have been disruptive for the R&D stage of development, it would have been incremental for the manufacture and marketing stages (Table 1). The policy decision not to regulate GM crops as if they were new plant varieties (the regulatory system most relevant to the seeds sector) but to build on the regulatory systems then in place for pesticides, drove development in the direction of the agrochemical industry sector (Tait, 2007).

Based on a well-informed plausible scenario for GM crop decisions made in the 1980s, if GM crops had been developed by the seeds sector we would have had a different set of first generation products (not tailored to the needs of the agrochemical industry), the technology would have been developed more rapidly, and we could have had a different European public response to this new technology.

Considering the future impacts of synthetic biology for the agro-biotechnology industry sector, over 20 years further on from its adoption of GM crop technology, the initial disruption has been assimilated within current business models and the impact of the introduction of synthetic biology, although more powerful, targeted and effective than the initial GM technology, is likely to be incremental across the board. For the industrial biotechnology sector, Table 1 shows that synthetic biology is likely to be disruptive at the R&D and manufacturing stages of product development, given that the industry is moving from chemicals-based to fermentation-based manufacturing facilities. However it will not be disruptive of existing markets – the company will still be selling a chemical product into its existing markets and these products will continue to be regulated through the chemicals regulatory system (REACH), or other product-specific regulatory systems, e.g. for foods or pharmaceuticals.

Table 1. Disruptive and incremental impacts on company business models.

Timescale	Industry sector	Technology	Disruptive / Incremental Change		
			R&D	Manufacture	Markets
1970s-80s	Agro-chemicals	Pesticides	Established	Established	Established
1980s-90s	Ag-biotech	GM crops	Disruptive	Disruptive	Disruptive
1980s-90s	Seed industry	GM crops	Disruptive	Incremental	Incremental
2000s-10s	Ag-biotech	Synthetic biology	Incremental	Incremental	Incremental
2000s-10s	Industrial biotechnology	Synthetic biology	Disruptive	Disruptive	Incremental

Box 4. SBLC (2016) case studies

Early stage applications of synthetic biology:

1. Devices for the detection of, for example, food spoilage or arsenic in drinking water;
2. Using microbial cell factories or GM plants to make novel proteins, artificial enzymes, omega-3 oils, hydrocarbons, propane, a cholesterol-lowering drug, menthol, grapefruit flavour, new antibiotics;
3. Modifying cereal crops to fix nitrogen;
4. Developing software to bring design for manufacturing to bio-engineering;
5. Genetically engineered cellular robots to attack cancer;
6. Control of insect-transmitted diseases using genetically modified mosquitos;
7. Developing organoids for animal-free drug testing; and
8. Single cell analysis systems for drug discovery.

Box 4 summarises the range of expected future applications of synthetic biology presented as case studies in the SBLC (2016) Report *Biodesign for the Bioeconomy*. The microbial cell factories described in (2) will deliver products to be sold through existing markets with well-functioning existing regulatory systems. The only disruption in these cases will be to the manufacturing process (a shift from a chemical refinery to a fermentation vat) with the requirement for regulators to adapt the regulations and standards for Good Manufacturing Practice (GMP).

Examples 3 and 6 in Box 4 could create new markets or disrupt existing markets, but the

modification of cereal crops to fix nitrogen is unlikely to be deliverable within 5 – 10 years. There are currently no insect transmissible diseases in the UK or Ireland that are considered as targets for a GM insect control strategy, although controlling ticks that spread Lyme's disease could become an attractive proposition. New detection devices based on synthetic biology (1) could be disruptive of existing markets but their development is seriously inhibited by current GM regulations in Europe and unless there is adaptation of these regulations they are unlikely to be manufactured or available in the EU⁴.

Other examples in Box 4 (4, 7 and 8) will support existing or new value chains for product manufacture so will be enabling of new developments but will not themselves be disruptive in the sense of requiring new approaches to product regulation.

In addition to the case studies from the SBLC (2016) strategy report, several crop developments relevant to the UK and Ireland, could potentially be available within 5-10 years, developed using GM and AIB-related techniques. Examples include: modified potatoes that are resistant to blight and will be less reliant on fungicide sprays to control the disease (Jones *et al.*, 2014); or functional foods such as the 'purple tomato' produced by the John Innes Centre that will be a cheaper food source for the anthocyanins that are beneficial to health⁵. Such advances are not likely to be considered disruptive of existing GM-based industry sectors and could contribute to the bioeconomy and, in the case of the potato, benefit the environment.

⁴ J. Ajioka, University of Cambridge, personal communication.

⁵ <http://www.bbsrc.ac.uk/documents/natures-factories-purple-tomato-pdf/>

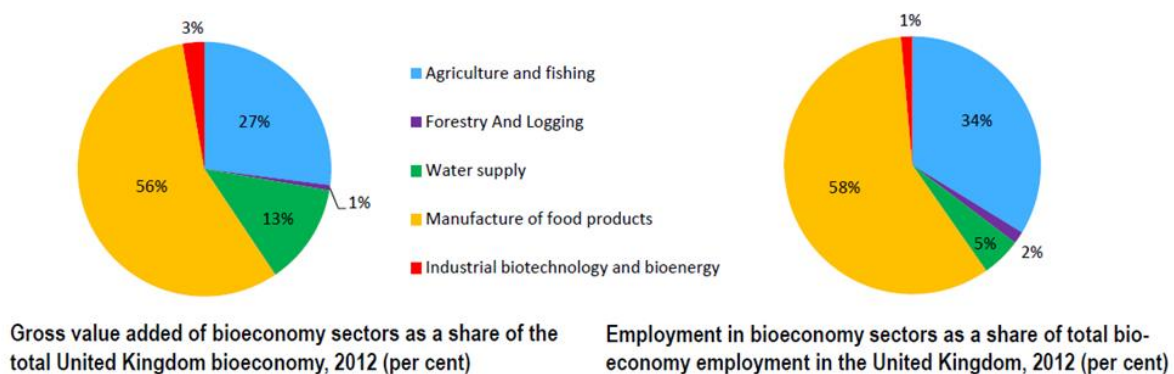
2.2 Scale and impact of synthetic biology related developments

The 21st century has been described as “the century of biotechnology” (Rifkin, 1998), in anticipation of a new industrial revolution, following on from the information and communication technologies (ICT) revolution that arose in the late 20th century. The Organisation for Economic Cooperation and Development (OECD) has been a prime mover in analysing and projecting likely futures for this revolution - “From a broad economic perspective, the bioeconomy refers to the set of economic activities relating to the invention, development, production and use of biological products and processes. If it continues on course, the bioeconomy could make major socioeconomic contributions ... to improve health outcomes, boost the productivity of agriculture and industrial processes, and enhance environmental sustainability.” (OECD, 2009).

The current scale of the UK bioeconomy is estimated to be least £150 Bn Gross Value Added (GVA), potentially increasing by a further £40 Bn over the coming decade and it supports approx. 600K jobs (Chambers *et al.*, 2015). Synthetic biology is expected to transform the sustainability and productivity of the industries that contribute to the bioeconomy. However, as noted in the Innogen Centre contribution to the OECD *Bioeconomy to 2030* report (Tait *et al.*, 2007), whether this is realised in the future will depend, among other things, on the nature of the regulatory and governance systems imposed on the development, marketing and use of these technologies.

A primary role for synthetic biology, as a platform technology, is seen to be facilitation of future contributions to the bioeconomy, with frequent references to the potential for this innovation to be disruptive – a move from an old-style approach involving harvesting resources that are cheap and plentiful to managing resources that are scarce and valuable⁶. The Chambers *et al.*, (2015) analysis of the impact of the bioeconomy on the UK economy (Figure 1) differentiates the value of the direct bioeconomy (the sectors that actually produce bio-based products), alongside those of the upstream bioeconomy (providing inputs to the direct bioeconomy) and of the downstream bioeconomy (using the outputs of the direct bioeconomy) (Figures 2 and 3). However, as noted above, the early impacts of AIBs are likely to be mainly incremental rather than disruptive. Also, of the sectors identified in Figure 1, the relatively small industrial biotechnology sector is the only one currently considering major investments in AIBs. The food sector could currently benefit from these technologies but, like agriculture and fishing, for a variety of reasons, it is not likely to be an early adopter.

Figure 1. Contribution of the direct bioeconomy to the UK economy (Chambers *et al.*, 2015)



⁶ www.sixthwave.org

Figure 2. Descriptive summary of the UK bioeconomy (Chambers et al., 2015)

<p>The direct bioeconomy</p> <p>The bioeconomy comprises those sectors that produce bio-based products – forestry, agriculture, industrial biotechnology, water supply and food manufacturing.</p> <p>It provides £36.1 billion in gross value added (2 per cent of the national total), 600 thousand jobs and is a vital part of the British economy.</p>	<p>Upstream / downstream impacts</p> <p>Upstream activities are generated by the bioeconomy's inputs demand. Downstream activities are those dependent on its outputs.</p> <p>Combined with spending by bioeconomy employees, they add a further £116.5 billion in gross value added (8 per cent of the national total) and 3.4 million jobs.</p>
<p>Geographical spread</p> <p>Unlike some regionally concentrated industries, the bioeconomy generates significant value across the whole country.</p> <p>Research and development means that the United Kingdom is one of the leading nations in many spheres of the bioeconomy from biopharmaceuticals to agriculture to energy.</p>	<p>Future prospects</p> <p>The bioeconomy and related sectors is one of the key growth areas for the economy because many of its industries are at the cutting edge of current scientific innovation.</p> <p>The bioeconomy is also going to be critical in creating an economy that is environmentally sustainable and run on low carbon emissions.</p>

Box 5. OECD: Bioeconomy to 2030 (OECD, 2009)

...biotechnology could contribute up to 2.7% of 2030 GDP in OECD countries ... and even more in non-OECD countries.

...by 2015...virtually all new drugs, about half of major crops around the world, and an increasing number of everyday products will be produced using biotechnology (perhaps an over-optimistic projection)

The bioeconomy offers technological solutions for many challenges facing the world...but achieving its potential will require appropriate national, regional, and in some cases, global policies.

In the longer term, the emerging bioeconomy will be significantly influenced by technological developments, **regulatory conditions***, intellectual property, human resources, **social acceptance***, market structure, and **business models***...addressing these needs to start today.

***Our emphasis, particularly relevant to this report**

The largest industry sectors in the direct bioeconomy (agriculture and fisheries, forestry and logging, water supply, food and drinks) together deliver £35.14 Bn to the UK economy, compared to industrial biotechnology (£995 M). Yet, industrial biotechnology is the only large scale industry sector that currently envisages an important role for synthetic biology in its future development (US National Research Council, 2015; SBLC, 2016). The other industry sectors described in Figure 2 are all somewhat conservative and so far reluctant to adopt AIBs. If the UK bioeconomy is to benefit from the potential contributions of synthetic biology (OECD, 2009) (Box 5), regulatory conditions and societal acceptance are among the most important factors that will need to be addressed. Figure 4 describes how this contribution is expected to operate, from academic research, through the synthetic biology enabling platform, to a broad range of industry sectors. The latest report from the UK SBLC (2016) further charts the potential contribution of synthetic biology to the bioeconomy (Box 6).

Box 6. UK SBLC (2016) Strategy Report: Contributing to the future bioeconomy

Synthetic biology provides a rapidly advancing capability to develop solutions to key challenges across the bioeconomy, spanning health, chemicals, advanced materials, energy, food, security and environmental protection. In recent years, the concept of a bioeconomy has evolved with potential for rapid and significant growth. Several countries have developed explicit bioeconomy strategies, reflecting the potential for biology as an economic force. Although there is currently no official UK bioeconomy strategy, the size of the UK bioeconomy is currently estimated to be worth at least £150bn GVA, potentially increasing by a further £40bn over the coming decade. Synthetic biology currently plays a small role in the overall bioeconomy but lies at its innovative heart. The development of higher-level biodesign capabilities could become a critical component of productivity and UK competitiveness in years to come, especially when international market growth opportunities are taken into account. Close links have been forged between the SBLC and the Industrial Biotechnology Leadership Forum (IBLF) and the Agri-Tech Leadership Council (ATLC), to ensure alignment between the role and potential value of synthetic biology and this broader vision for the UK bioeconomy.

Figure 3. GVA from direct activities of the bioeconomy in the UK (2012) (£M) Chambers et al., 2015)

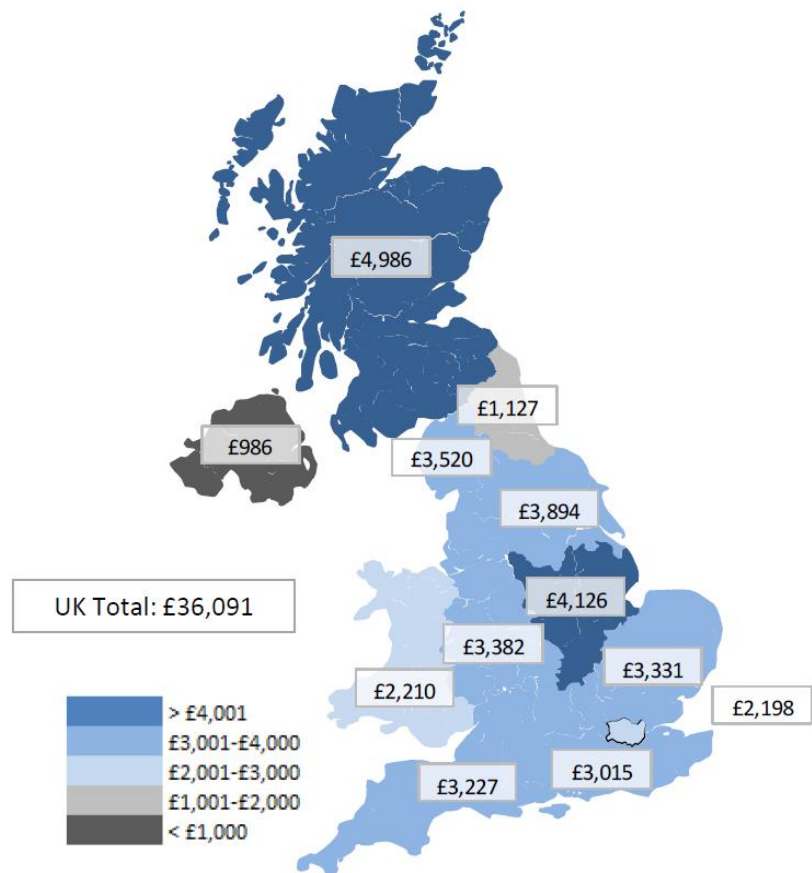
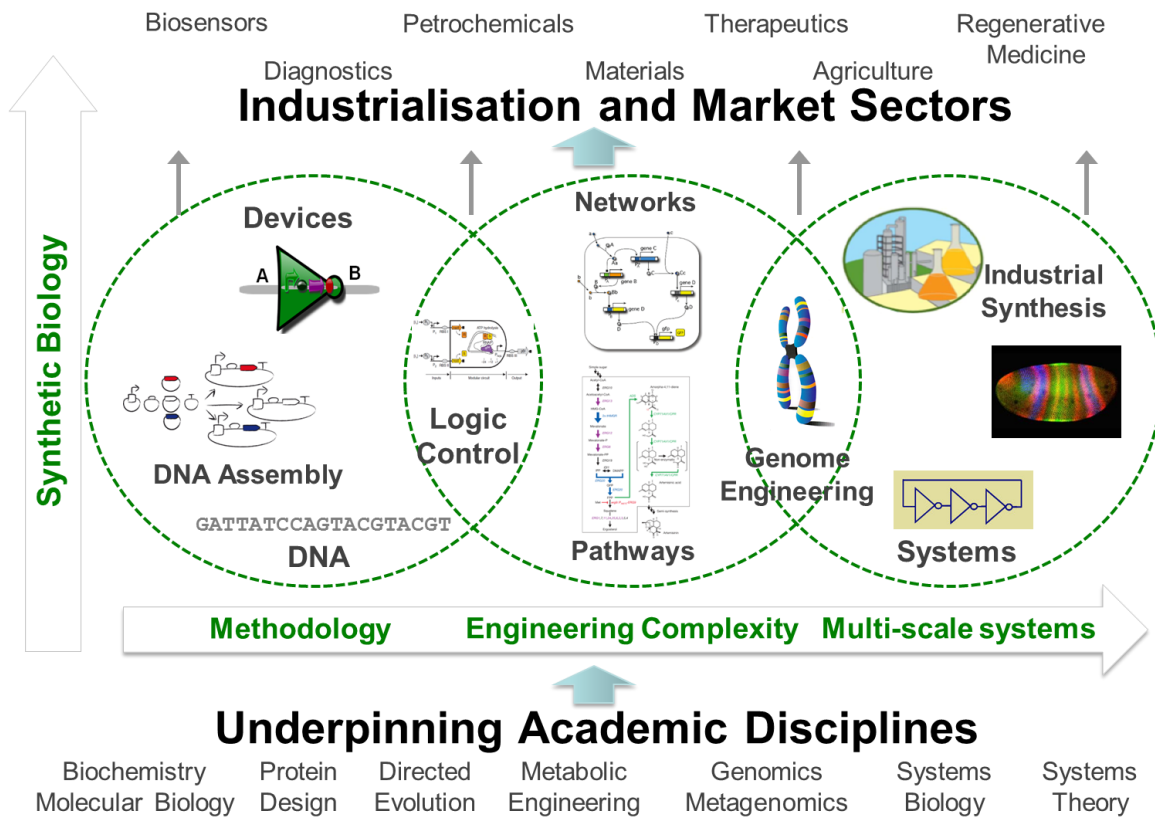


Figure 4. Contribution of synthetic biology to the bioeconomy (UK Synthetic Biology Coordination Group, 2012, p13)



These potential benefits to the economy and the environment can clearly contribute to sustainable development and to the overall goal of reducing the human ecological footprint (Wackernagel and Rees, 1996), bringing synthetic biology into focus as a potentially major factor in the ‘circular economy’, as espoused by the governments of all the EAs involved in ShARE (Natural Scotland, 2016; Chamberlain *et al.*, undated; HoC Environmental Audit Committee, 2014; Mitchell and Doherty, 2015; EPA, 2014).

2.3 Innovation policy support for synthetic biology

There is considerable UK Government support for AIBs at the research stage and also translational funding to support early innovation stages of development to help small companies to cross the ‘valley (or valleys) of death’ (a term used to describe the lack of commercial investment at several stages in the development pathway for an AIB (Omidvar *et al.*, 2014; House of Commons (HoC) Science and Technology Committee, 2013). Mazzucatto (2011) has commented, as an economist, on the necessity for state support in the early stages of development of innovative technologies. The Innogen Institute has looked at this economic analysis from a more systemic perspective and pointed out that such state support for innovation will struggle to have the expected economic impact where, as in the case of life science innovation, regulatory systems are expensive, time consuming and difficult for companies, particularly small companies, to negotiate (Tait, 2007; Tait and Chataway, 2007) (see Section 3.6).

The following are some of the current UK Government financial support initiatives that are relevant to AIBs.

- **Eight Great Technologies.** The support for the UK's Eight Great Technologies was announced by the then Minister for Science in 2013⁷. Synthetic biology (with £88M investment) was included among these technologies and two other Great Technologies relevant for synthetic biology-related innovation were Agri-tech (£30M investment) and Regenerative Medicine (£20M investment). The inclusion of synthetic biology among the Eight Great Technologies has been a particularly important determinant of its success to date, including for example the recent announcement of the setting up of an Eight Great Technologies Investment Fund with a target of £300M⁸.
- **Scottish Innovation Centres:** In 2012, the Scottish Funding Council announced a £120M fund, to set up Innovation Centres⁹ to link academics with industry in the development of innovative new technologies. The two most relevant to synthetic biology are the Industrial Biotechnology Innovation Centre (IBioIC) and the Stratified Medicine Innovation Centre.
- **Catapults:** A group of Catapult Centres¹⁰ has been set up to "...transform the UK's capability for Innovation and drive future growth" through a combination of state and commercial funding, the most relevant for synthetic biology being Cell and Gene Therapy, Medicines Discovery and Precision Medicine.
- **Catalysts:** Significant amounts of government and commercial funding are also being invested in a series of Catalysts¹¹ designed to support interdisciplinary research initiatives and early stage commercial development, the most relevant to synthetic biology being the Biomedical Catalyst, the Industrial Biotechnology Catalyst, the Agritech Catalyst and the Energy Catalyst.

The Synthetic Biology Leadership Council (SBLC), another UK Government policy initiative in support of synthetic biology, was set up to provide a governance body to assess progress, update recommendations and shape priorities for future implementation of synthetic biology in the UK. It provides strategic coordination between the funding agencies, the research community, industry, government sponsors and other stakeholders. The SBLC Governance Subgroup¹² has the task of providing support and advice to the SBLC on governance, policy and regulation, citizen and stakeholder engagement, and communication, as they relate to research and technology development in synthetic biology. Along with the Agri-Tech Leadership Council and the Industrial Biotechnology Leadership Forum the SBLC works to ensure that the UK effectively harnesses its world-class research and innovation base to develop the bioeconomy.

2.4 Future prospects for AIBs

Although the contribution of synthetic biology to the bioeconomy is currently modest, the scale and reach of government policies in this area are an indication of the determination to ensure that the UK is able to benefit significantly in future from its current investments in the basic

⁷ <https://www.gov.uk/government/speeches/eight-great-technologies>

⁸ <http://www.zgc.gov.cn/document/20151228161054343989.pdf>

⁹ <http://www.sfc.ac.uk/Priorities/Innovation/InnovationCentres.aspx>

¹⁰ <https://www.catapult.org.uk/>

¹¹ <https://interact.innovateuk.org/-/catalysts>

¹² <https://connect.innovateuk.org/web/synthetic-biology-special-interest-group/governance-sub-group>

science and early translational stages of development. The government funding initiatives outlined above are undoubtedly having an impact on the scale of activity in this area in the UK. However, as with all new areas of innovation, there has been considerable hyping of expectations around the technology, partly designed to secure funding and political support. However, whether and how rapidly this potential is realised will depend on a broad range of factors: (i) Kwok (2010) pointed to ‘five hard truths for synthetic biology’, mainly related to the greater complexity and unpredictability of dealing with biology rather than more straightforward engineering in manufacturing processes; (ii) the economic realities of dealing with synthetic biology can lead to unexpected outcomes, for example the recent closure of Sanofi’s manufacturing facility using synthetic biology to produce the anti-malarial drug artemisinin, because of low-price competition from farmers growing the *Artemisia* plant in the traditional manner (Peplow, 2016¹³); and perhaps most important the governance processes we put in place for AIBs in future (Tait, 2008).

Thus, although AIBs are likely to benefit the UK economy, as noted in the following sections there will be numerous policy and regulatory opportunities either to constrain or encourage this process. Innovation processes rarely proceed according to plan and eventual success will depend on long term commitment by governments and industry, and a willingness to adapt both innovation processes and governance systems to unexpected outcomes, positive or negative.

3 Regulation and governance of GMOs and future AIBs

This section summarises the regulatory systems currently in place for GM-related technologies, given that they are likely to be applied to AIBs in future, and indicates how they are seen to be performing in light of our current understanding of the risks and benefits of GMOs. The precautionary principle (PP) is an important feature of EU environmental regulation and its role in the governance of GMOs in Europe is also assessed, along with evolving public attitudes to the technology. The EU regulatory system has been the subject of sustained criticism from research organisations, lawyers, government bodies involved in advising on regulatory issues and academic researchers, and some of these arguments are also summarised here.

3.1 Potential environmental benefits of AIBs

The impacts on the bioeconomy outlined in Section 2 are supported by a range of government policies because they are seen, among other things, to have the capacity to improve the ecological footprint of important industry sectors, for example in mitigating climate change, improving food security and reducing agriculture-related pollution (Figure 5). Although outside the scope of this report it is useful to note that Africa and Asia are seen as important potential beneficiaries of these new more advanced AIBs in their agricultural systems and Whitty *et al*, (2013) have called for a more rational debate on this potential that is not dominated by Europe’s politicised arguments.

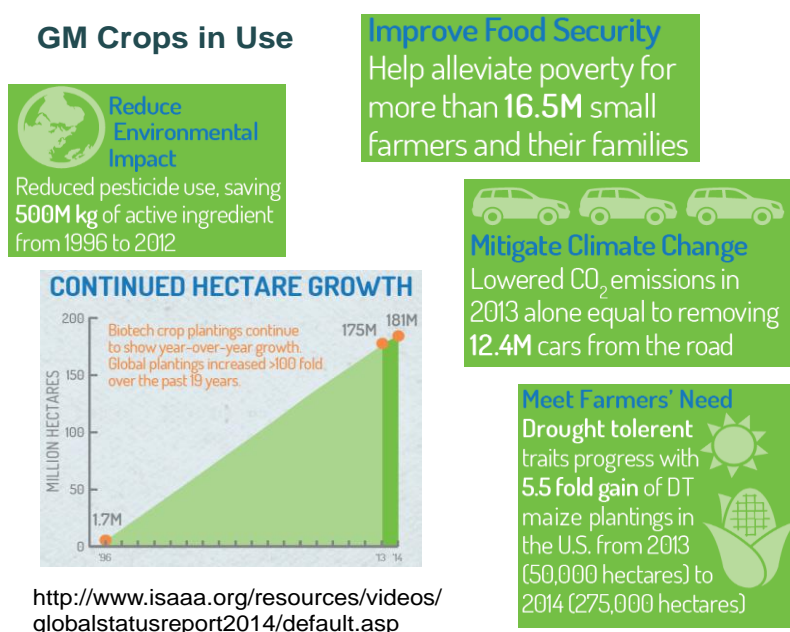
Overall current synthetic biology developments are seen as *incremental* innovations, based on more powerful and accurate GM-related techniques than we have had at our disposal in the past, but not leading to radically new challenges to existing markets or regulatory systems (Section 3.5). Two areas where synthetic biology could have more potentially *disruptive* implications both involve ecosystem related applications:

¹³ Interestingly, there is no reference to this event on the Sanofi website.

- i. Synthetic biology is being considered as an aid to saving endangered species and returning extinct ones. This issue is controversial and Redford *et al.* (2013) have analysed both sides of the argument, noting that both the problems and the solutions are ‘wicked’ “... messy, intractable, subject to multiple interpretations, and for which solutions at present are not evident or inscrutable”.
- ii. A recent development of synthetic biology, the gene drive, can be seen as raising a similar set of issues to those addressed by Redford *et al.* (2013) although the aim here is species elimination, rather than species introduction. This technique has been proposed, for example, to eliminate an invasive species from an ecosystem, and also to remove disease-carrying insects such as mosquitoes transmitting malaria, dengue fever or zika virus (US National Academies of Sciences, Engineering, and Medicine, 2016).

Neither of these developments is likely to move beyond the basic research stages within the next 5 – 10 years, and it is not yet clear how these more disruptive innovations will be regulated in future. However, the development pathway in both cases is likely to be through a one-off state-supported initiative, given that these applications do not have a conceivable commercially viable business model that would support the involvement of a company, other than in partnership with a government initiative. It is important to distinguish gene drive technology, expected to lead to permanent elimination of a species, from the business approach developed by the company Oxitec, currently being applied in several disease-affected areas of the world with the approval of the relevant governments and of local populations¹⁴ (Lacroix, *et al.*, 2012), which will require repeated release of the sterile male mosquitoes.

Figure 5. Scale of GMO uptake: environmental and other benefits



3.2 Potential environmental hazards of AIBs

The Statement of Requirements for this report refers particularly to potential risks of synthetic biology and the implications for environmental regulation. The techniques defined in Box 1 under the heading of AIBs are considered to be part of the GM and synthetic biology toolbox and they

¹⁴ <http://www.oxitec.com/>

will be considered together here, with the exception of the gene drive¹⁵. Where AIBs are used in the manufacture of non-living products they can be seen as ‘platform technologies’, sets of tools and techniques that can lead to the development of innovative products and processes that are likely to be covered by existing regulatory systems for chemicals, foods and drugs, involving contained use of GMOs. Where the innovation involves deliberate release of a living modified organism and will be regulated on that basis, regulators could build on the experience of a number of countries that are ahead of the EU in this respect and adapt regulatory systems to new circumstances. The main difference between synthetic biology and GM techniques is that, whereas GM involves the transfer of individual genes from one species to another, synthetic biology and gene synthesis assemble complex novel genomes from a set of standardized genetic components to deliver the target molecules or effects in a more predictable and efficient manner than was possible with the more primitive GM approaches.

Although some of these techniques are not yet included under the legally-based regulatory system in place for GMOs this is expected to be the regulatory precedent that will be applied to all AIBs in future, with modifications where necessary. There is no evidence base for the prediction that the greater power and precision of AIBs will, in commercial application, lead to new or increased environmental hazards. Indeed, their greater precision and hence their greater predictability may lead to less uncertainty about future hazards and a greater ability to regulate them on the basis of scientific evidence rather than conjecture and speculation (see Section 3.3).

This is not to advocate complacency in the face of potential hazards arising from future developments of AIBs and regulators and innovators will need to remain vigilant but at the same time to build on the experience of the safe development of first generation GM technologies under a range of regulatory approaches in many parts of the world.

One important area of concern relates to biosecurity threats arising from AIBs, i.e. malicious use by those intent on causing harm, or accidental misuse in the course of legitimate scientific research, and the anticipated scale of this threat has a much higher profile in the USA than in Europe. The greatest, and least controllable, threat is likely to come from state-sponsored terrorism and, while there is general agreement that these risks remain extremely low¹⁶, UK industrial providers are being vigilant. For example, consortia of providers have instigated gene synthesis order-screening procedures¹⁷, and the recently established DNA foundries in the UK have signed-up, or are in the process of signing-up, to such consortia (SBLC, 2016). It is also important to understand that one of the best defences against future accidental or deliberate misuse, or indeed against a much more likely naturally occurring pandemic disease, is to have appropriate diagnostics, vaccines and antibiotics already available or able to be developed in a very short timescale. Synthetic biology tools, along with appropriate regulatory adaptation to facilitate rapid responses, are the key to delivery of this defence (Lowrie and Tait, 2011; Presidential Commission for the Study of Bioethical Issues, 2010; SBLC, 2016).

¹⁵ Gene drives, given the intentional spread of the modified organism within ecosystems, may require a different regulatory approach from those currently in operation for GM and other closely related biotechnologies.

¹⁶ Workshop report - Synthetic Biology and Biosecurity.

<https://www.kcl.ac.uk/newsevents/news/newsrecords/docs/Jefferson-et-al-2014-Synthetic-Biology-and-Biosecurity.pdf>

¹⁷ *Screening framework - guidance for providers of synthetic double-stranded DNA.*

<http://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf>

3.3 The role of the precautionary principle (PP) in the governance of AIBs in the EU.

The PP was proposed in response to a series of unexpected hazards arising from chemicals that had been approved through relevant regulatory systems, for example the impact of organochlorine insecticides on the breeding success of top predators. Emerging from a German approach to environmental regulation (von Moltke, 1987), a case was made for its adoption as the basis of the regulatory system for GMOs in the UK (Royal Commission on Environmental Pollution, 1989). The UK legislative process was then influential on subsequent developments in the EU (Tait and Levidow, 1992) and the United Nations Convention on Biological Diversity (CBD).

Over time the PP began to acquire a number of interpretations related to the degree of precaution to be implemented, and the Commission of the European Communities (2000) issued advice on its adoption, supplemented recently by some additional guidance¹⁸ (Box 7), noting that “... decision-makers are constantly faced with the dilemma of balancing the freedom and rights of individuals, industry and organisations with the need to reduce the risk of adverse effects to the environment, human, animal or plant health”.

Box 7. EU Guidance on Implementation of the Precautionary Principle

The adoption of the PP is appropriate where “...scientific evidence is insufficient, inconclusive or uncertain and there are indications **through preliminary objective scientific evaluation** (our emphasis) that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection”. The document published by the Commission of the European Communities (2000) emphasised the need to find a balance so that “... proportionate, non-discriminatory, transparent and coherent actions can be taken” based on:

- examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis);
- review in the light of new scientific data; and
- assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment.

An update (2015) on the use of the PP in the EU (<http://eur-lex.europa.eu/legal-content/EN/Txt/?uri=URISERV:132042>) stresses that the PP can never be invoked to justify arbitrary decisions, requiring the following elements relevant to the development of AIBs:

- examination of the benefits and costs of action or lack of action;
- identification of potentially adverse effects;
- evaluation of the scientific data available;
- consideration of the extent of scientific uncertainty;
- participation of all interested parties in the study of precautionary measures, after the results of a scientific and/or risk evaluation have been made available;
- review of measures in light of scientific developments.

These guidelines, along with the expected regulatory principles of proportionality and adaptation (Tait and Banda, 2016a, b) enshrined in these European Commission documents, have not yet been applied in Europe in the context of environmental release of living GMOs, largely because of political constraints (Mittra *et al.*, 2014) (although the contained use of GMOs has presented

¹⁸ <http://eur-lex.europa.eu/legal-content/EN/Txt/?uri=URISERV:132042>

few such problems). Indeed, much more extreme versions of the PP have been invoked by Non-Governmental Organisations (NGOs) commenting on GM and AIB-related developments and these extreme interpretations could be influential on European public opinion related to AIBs^{19,20}.

Any regulatory decision to use the precautionary principle as a basis for additional restrictions on the development of AIBs should first undertake the kind of review recommended in Box 7. It is relevant to note that, if the current European interpretation of the PP had been in operation globally for the development of GMO technologies, we would have had no evidence for their safety or for any of the benefits.

3.4 Stakeholder engagement and public attitudes to GMOs and AIBs

The deliberate release, but not the contained use, of GMOs in the EU has been very contentious. For example, a 2005 Eurobarometer survey (Gaskell *et al.*, 2006), found that there was widespread support for medical and industrial biotechnologies, but considerable opposition to agricultural biotechnologies in all but a few countries. When asked about GM food, a majority of the 50% of Europeans who had a settled opinion on the subject thought that GM food should not be encouraged – it was seen as not being useful, as morally unacceptable and as a risk for society (58 per cent opposed and 42 per cent supported the use of the technology). Supporters outnumbered opponents only in Spain, Portugal, Ireland, Italy, Malta, Czech Republic and Lithuania (Gaskell *et al.*, 2006). The lesson drawn for agri-food biotechnology was that unless new crops and products are seen to have consumer benefits, the public would continue to be sceptical about their use. Figure 6 gives more detailed information from this report, showing responses to different types of benefits incorporated within GM foods²¹.

There are hints in more recent surveys that public attitudes to current GM technologies are less negative than they have been in the past (Royal Society of Edinburgh (RSE), 2015). In a recent Ipsos Mori (2014) poll on Public Attitudes to Science, more people in the UK said that the benefits of GM crops are greater than the risks, by 36% to 28%. When asked about the statement whether “Genetically modified crops are needed to increase world food production,” 57% agreed against 15% who disagreed. When asked to consider a more general proposition that “We should not rule out any agricultural techniques or technologies that might help to increase world food production” 80% agreed against 9% who disagreed. However, these questions are phrased in such a way as to invite a positive response, described as ‘leading statements’.

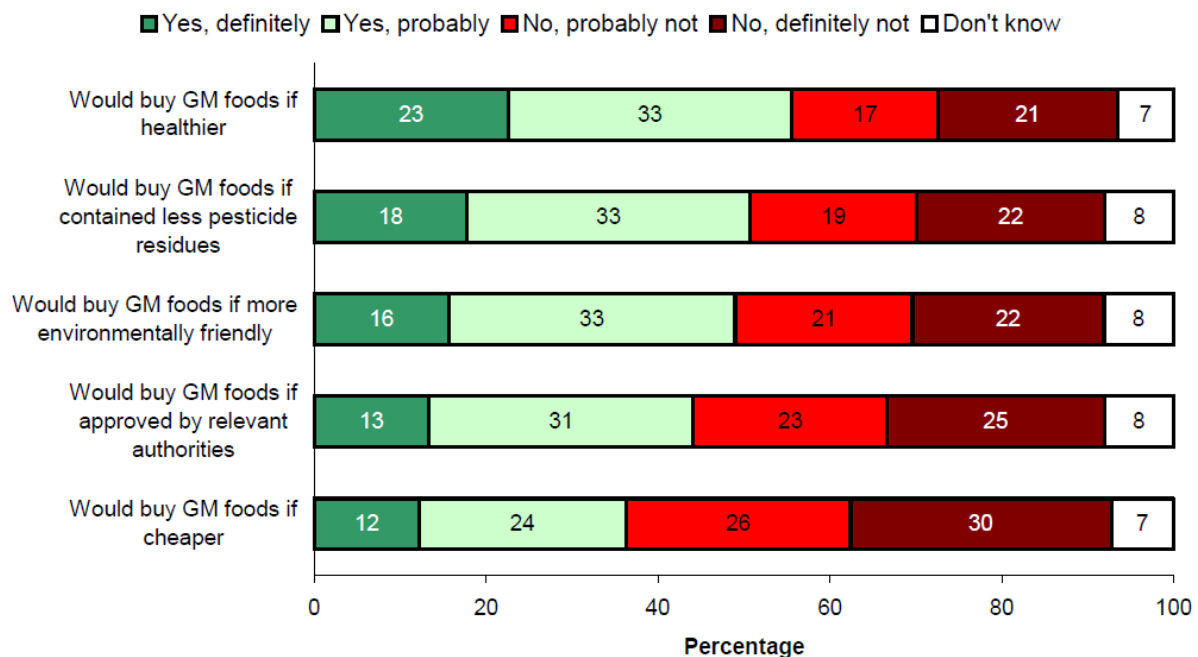
¹⁹ <http://www.etcgroup.org/content/extreme-genetic-engineering-introduction-synthetic-biology>

²⁰

http://www.synbioproject.org/process/assets/files/6620/_draft/principles_for_the_oversight_of_synthetic_biology.pdf

²¹ The summary of the report by Gaskell *et al.* (2006, p4) states that these figures refer to the 50% of the survey respondents who had a settled opinion on the subject, equating to 29% of the total survey population opposed to the use of the technology and 21% in support, but this factor (very relevant to the interpretation of the data) is not referred to elsewhere in the report.

Figure 6. Reasons for buying GM foods (Gaskell et al., 2006, pp 4 and 22).



A smaller unpublished survey commissioned in 2012 by the British Science Association as part of National Science and Engineering Week²² demonstrated similar levels of *decline in opposition to*, along with a *decline in support for*, GM foods in general, with citizens having moved more into the neutral/don't know categories compared to previous surveys. Where there were significant public benefits, for example, the production of rice crops with enhanced levels of vitamin A, in this survey, over 64% supported the use of such a crop, with only 13% opposed. Similarly, producing wheat crops with reduced susceptibility to aphids, thereby reducing the use of pesticides, was also supported by 58%, with only 15% against, but again these are leading statements (RSE, 2015).

A detailed analysis of opinion polling data is beyond the scope of this report. However, although the degree of negativity may be declining, there is still a vociferous minority of respondents (the above quoted data would suggest around 15-20%) who are likely to oppose the development of GM technologies, no matter what the benefits. This relates to an important factor that is essential to understanding how to interpret public survey data and is ignored in almost all surveys – the psychological foundation of the opinions being expressed (Tait, 1988; 2001; 2014). Table 2 summarises the different characteristics of a stakeholder dialogue when participants' opinions are based mainly on 'what is in my interests' (left hand side of the table) and on 'my deeply held values or principles' (right hand side of the table). In the middle, and not to scale, are the uncommitted members of the public who either don't know or don't care (or both) about the issue under discussion, variable in number but often around 60%.

Table 2 can be seen as summarising the criteria that would enable participants in a dialogue or its organisers to recognise the basis on which different parties are contributing (Tait, 2001) and by these criteria the public and stakeholder dialogue in the EU has been led and framed by participants with ideological, value based perspectives. Although presented here for clarity as a

²² <http://www.theguardian.com/environment/2012/mar/09/gm-food-public-concern>

dichotomy, it is important to stress that stakeholder motivations will always entail a complex mixture of factors. In many areas of stakeholder dialogue, this dichotomy may not even be apparent. However in the case of the European dialogue on GM crops, this does correspond with the observed situation. The key to understanding the percentage of a population that is engaging with an issue from an ideological perspective is to focus on those who continue to give negative responses when asked leading questions about positively beneficial applications of a technology, e.g. the 15% who disagreed that “GM crops are needed to increase world food production” in the Ipsos MORI (2014) poll described above.

For participants on the right hand side of Table 2, the only evidence considered relevant to a decision is information that supports the case they want to make and, on occasion, research conducted with the intent to deliver such supporting evidence has been found to be invalid (e.g. Seralini *et al.*, 2012). The intractable nature of EU public opinion is partly due to the attention that has been given in media and policy circles to opinions that are based on deeply held, probably immutable values backed up by all the other features represented on the right hand side of Table 2. It could also be claimed that the introduction of the precautionary principle (Section 3.3) was an important factor in enabling these value-based agendas to gain so much traction on EU policy decision making (Tait, 2014).

Table 2. Characteristics of environment and technology-related conflicts

Interest based conflicts - minds	Uncommitted members of the public ~ 60%	Ideology based conflicts - hearts
Restricted to specific developments		Spreads across related and unrelated developments
Location-specific, locally organised		Organised nationally or internationally
Can be resolved by: <ul style="list-style-type: none"> • Giving information • Giving compensation • Negotiation 		Very difficult to resolve: <ul style="list-style-type: none"> • Information = propaganda • Compensation = bribery • Negotiation = betrayal
Giving of concessions leads to mutual accommodation		Giving of concessions leads to escalation of demands
Protagonists do not have a higher level cause/agenda		Protagonists look to recruit supporters to a higher level cause

This generally unrecognised distinction is key to understanding how to interpret and act on the data from surveys of public opinion. It will, for example determine the extent to which public opinion is likely to change in response to new evidence of the hazards, safety or benefits of existing and new AIBs. Where there is a significant proportion of ideologically based opposition or commitment to a particular technology, dialogue can increase polarisation of opinion rather than leading towards consensus (Sunstein, 2009). It also raises the question, “Under what circumstances is it valid in a democracy to permit a minority of the population to determine the opportunities (economic and life-style related) available to the rest of the population?”

Finding a way to guide the dialogue on AIBs towards a more equitably evidence-based approach will be necessary if the UK and RoI are to benefit from the potential contribution of these technologies to the bioeconomy, including devising regulatory systems that are proportionate to the expected hazards. A stance of **equitable scepticism**, towards the arguments of companies attempting to serve their economic interests (left hand side of Table 2), and towards advocacy groups intent on furthering their values (right hand side of Table 2), might be a good starting point. Equitable scepticism as a basis for decision making could be a potentially useful counter-balance to the more frequent emphasis on trust as an aspirational goal for authority figures.

There have been fewer studies of citizen views on synthetic biology and industrial biotechnology but those available have been summarised in two reports from Sciencewise, a government funded programme to support the role of public dialogue in policy making, providing advice and guidance to help policy makers to understand and take into account the views and values of the public in the development of policy involving science and technology (Boxes 8 and 9).

Box 8. Public views of synthetic biology (Sciencewise, 2013)

Sciencewise noted that there are “a number of major possible social, ethical and environmental risks and challenges, including bioterrorism, commercial monopolies, and the philosophical and religious concerns associated with creating artificial life” but that overall there is low public awareness of the sector.

Commonly held views include:

- extremes; it is both exciting and scary
- the need for regulation and control which could keep up with developments in the sector
- synthetic biology could lead to the transgression of nature
- optimism is high: the technology presents solutions to some of the world’s major challenges
- the motivation of scientists in this sector has been questioned
- synthetic biology could produce big winners, and big losers
- given that the public consider themselves powerless to influence the sciences more generally, scientists have a responsibility to consider the wider implications of their work

Box 9. Public views of industrial biotechnology (Sciencewise, 2015)

Public opinion on industrial biotechnology is broadly positive but fluctuates in response to international events and technological developments. There is little recent in-depth research.

Public opinion is highly dependent on context, the technology under consideration, and the question asked.

While there is awareness of the potential risks, the overall attitude to industrial biotechnology is positive. Public scepticism about its wide-scale adoption is often linked with mistrust of government and industry.

Medical applications viewed more favourably than agricultural ones but people are not uncritically positive or negative about either technology.

There is concern about the use of bioenergy, partly due to the implications of land use for fuel crops.

Little is known about public opinion on the emerging third and fourth generation biofuels derived from algal technologies, or genetically engineered plants.

The evidence quoted above that European public attitudes to GM and related technologies are becoming more neutral and less polarised, could provide an opportunity for policy makers and regulators in the EU to focus their attention on actual and potential hazards and benefits and their probabilities, rather than on politics and public attitudes when making decisions on regulatory questions (Tait and Barker, 2011). Treating the EU regulatory process for GM as the precedent for regulation of synthetic biology, and probably other AIBs, is a logical choice in most of the world but, in the EU there is a potential for this decision to lead to serious and unnecessary inhibition of the development of AIBs unless the political biases involved in the operation of the EU system are removed (Tait and Barker, 2011; Tait, 2009b; Mittra *et al.*, 2014).

3.5 Current regulatory systems for GMOs

In the EU, and hence also in the UK, the regulatory system for AIBs is likely to be based on that currently in place for GMOs where the most important regulatory distinction is between GMOs in *contained use* and their *deliberate release* to the environment.

3.5.1 Contained use

Where GMOs are contained within a fermentation vat or a glasshouse or other such facility, and only the resulting, non-living products are circulated beyond containment, these products will be regulated as foods, drugs, fuels or chemicals and will be covered by the appropriate regulatory systems for these products. The regulatory system that applies to their production will be the EU Contained Use Directive (Directive 2009/41/EC) and the UK Contained Use Regulations (Genetically Modified Organisms (Contained Use) Regulations 2014) developed to ensure our compliance with the EU Directive. To summarise the UK arrangements for implementation of these Regulations, as stated on the HSE website²³,

The UK competent authority (CA) for the Genetically Modified Organisms (Contained Use) Regulations (GMO(CU)) comprises representatives of the four responsible authorities in the UK. The GMO(CU) 2014 regulations apply to England, Scotland and Wales. The GMO(CU) (Northern Ireland) 2015 Regulations apply to Northern Ireland.

In England and Wales, the Health and Safety Executive (HSE) and the Secretary of State for the Department for Environment, Food and Rural Affairs (DEFRA) acting jointly form the competent authority. The functions are delegated to HSE and DEFRA officials. Officials from the Welsh Government are included in any matters relating to Wales.

In Scotland, the competent authority comprises Scottish Ministers and HSE acting jointly and similarly, and these functions are delegated to HSE and Scottish Government officials.

In Northern Ireland, the competent authority is the Health and Safety Executive for Northern Ireland (HSENI) and the Department of the Environment, acting jointly. HSENI officials are provided with technical support from HSE, under an Agency Agreement.

The relevant UK advisory committee is the Scientific Advisory Committee on Genetic Modification (Contained Use) (SACGM).

The UK CA provides the mechanism by which agreement on policies related to GMO(CU)-related business will be sought.

There is a presumption that contained uses of GMOs present minimal hazard to the natural environment and the regulatory requirements are correspondingly less demanding than for

²³ <http://www.hse.gov.uk/biosafety/gmo/whos-responsible.htm>

deliberate release. However, some of the NGOs campaigning in this area are proposing that, for synthetic biology, contained uses of modified organisms should be subject to the same regulatory system as deliberate release²⁴. The main forum through which these representations are currently being made is the discussion on the need to revise the UN Convention on Biological Diversity (CBD) to take on board any additional risks that might be entailed in synthetic biology related developments. However, given the broad range of opinions being expressed in CBD-related fora (see Section 4.2) it would be surprising if such propositions were incorporated within future revisions to the CBD.

3.5.2 Deliberate release

Most relevant to the concerns of ShARE is the deliberate environmental release of living organisms modified using AIBs into the natural environment, for example a GM crop or a micro-organism developed for environmental remediation. The EU regulatory instrument is the Deliberate Release Directive (Directive 2001/18/EC), implemented in the UK through the Environmental Protection Act 1990, Section 111 and 112 and the Genetically Modified Organisms (Deliberate Release) Regulations 2002²⁵.

For the innovations listed in Box 4, using cells as factories (2) or for drug discovery (8) are clearly contained uses, whereas GM cereal crops (3) or mosquitoes (6) are clearly deliberate releases. However, the distinction between these two regulatory categories is not always clear cut. For the arsenic detection device (1), although the GM cells (the active component) are contained within the device and are regulated through the Contained Use Regulations, regulators are concerned that they could 'escape' into the natural environment due to an accident in use and so this is also being regulated under the Deliberate Release Directive. Also included under the Deliberate Release heading are GM viral vaccines and other medical treatments for humans or animals involving living modified organisms.

The UK Lead Territorial Competent Authority for Deliberate Release is the Department for Environment, Food and Rural Affairs (DEFRA), advised by the Advisory Committee on Releases to the Environment (ACRE)²⁶. Applications for approval to market a product (including crop seeds for cultivation, foods or feeds) are assessed and decided upon at EU level by the EU Food Safety Authority, while applications to release a GMO for research and development purposes are considered at national levels. The assessment process for GM release or marketing applications considers potential safety factors such as toxicity, allergenicity, and the fate of any possible transfer of novel genes to other organisms. The dossier of relevant information to cover these points is scrutinised by ACRE.

The Scottish competent authority²⁷ for deliberate release to the environment is the CAP Reform Crops Policy Branch at the Scottish Government, Agriculture and Food Division. Consents for releasing GMOs into the environment for research purposes are granted on a case by case basis by Scottish Ministers. A detailed risk assessment must be submitted to the CAP Reform and Crop Policy Team and is considered by ACRE. Scottish Ministers also consult Science and Advice for

²⁴ <http://www.etcgroup.org/content/extreme-genetic-engineering-introduction-synthetic-biology;>
http://www.synbioproject.org/process/assets/files/6620/_draft/principles_for_the_oversight_of_synthetic_biology.pdf

²⁵ <https://www.gov.uk/government/collections/genetically-modified-organisms-applications-and-consents>

²⁶ <https://www.gov.uk/government/collections/genetically-modified-organisms-applications-and-consents>

²⁷ <https://www.sasa.gov.uk/book/export/html/139>

Scottish Agriculture (SASA), the Health and Safety Executive, the UK Food Standards Agency and Scottish Natural Heritage.

In Wales, the relevant regulations are the Genetically Modified Organisms (Deliberate Release) (Wales) Regulations 2002 and the National Assembly for Wales is the relevant competent authority²⁸.

The relevant legislation in Northern Ireland is the Genetically Modified Organisms (Deliberate Release) Regulations (Northern Ireland) SR 2003/167 and release of a GMO would require consent from the Department of the Environment for Northern Ireland.

In Ireland²⁹, the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003 give effect to EU Directive 2001/18/EC on the deliberate release into the environment of GMOs. The Environmental Protection Agency (EPA) is the Competent Authority in Ireland for the implementation of the GMO Regulations on the contained use, the deliberate release and the transboundary movement of GMOs into the environment.

3.5.3 EU opt-out legislation

In 2015 the European Parliament and the Council amended Directive 2001/18/EC and approved Directive (EU) 2015/412³⁰ to allow Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory. This EU legislation does not permit the use of scientific evidence as the basis for decisions to reject the growing of GM crops, given that only those crops that have been approved as safe by the EFSA will be able to be grown, emphasising the confidence of the regulators in the safety of this technology.

Although ostensibly designed to permit individual nations to *reject* cultivation of approved GM crops on their territory, the legislation could also have the effect of *permitting* others to circumvent the political bias currently driving EU regulation of GMOs and to make their own decisions on whether to grow GM crops. This opportunity has resulted in different decisions in different countries involved in ShARE. While England has announced that GM crops will be grown on its territory, the decision for Wales, Scotland and Northern Ireland has been in the opposite direction. Ireland also made the decision to support the growing of GM crops. This situation adds to the complexity of the regulatory systems and the market context faced by developers of GM crops across the EU.

In a related legislative initiative, less relevant to environmental issues, the EU Parliament rejected a proposal to allow EU member states to decide for themselves whether or not to *import* Genetically Modified Organisms for use in food and animal feed.

3.5.4 International differences in regulatory systems for GMOs

Governance frameworks in different parts of the world have shaped the way regulatory systems for genetically modified organisms (GMOs) have evolved since the 1980s. The most striking differences are between those of the European Union (EU) and its constituent countries and the United States (US) (Tait, 2008). Internationally, the EU has been very influential in shaping the UN Convention on Biological Diversity (CBD) and the related Cartagena and Nagoya Protocols. On the other hand the US regulatory system has influenced and been more influenced by the Organisation for Economic Cooperation and Development (OECD). These differences have

²⁸ <http://www.legislation.gov.uk/wsi/2002/3188/contents/made>

²⁹ https://www.fsai.ie/legislation/food_legislation/gmos/regulating_gm_food_eu_ireland.html

³⁰ <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L0412&qid=1457367451353&from=EN>

persisted since the 1980s. Each system has in its turn influenced the regulatory systems of other countries: similar approaches to that of the US are in operation in much of South America; while the European system has been most influential in Africa, although this has recently begun to change³¹. The Canadian regulatory system is regarded in international comparisons as the most appropriately adapted to managing the hazards of GMOs (Mittra *et al.*, 2014).

The reasons for the emergence and persistence of these different regulatory systems for GMOs are complex. The EU environmental lobbies have had greater political power than in the US and they have used this to achieve incorporation of a strong version of the precautionary principle into EU (and also UN) legislative systems (see Section 3.3). This in turn enabled these lobbyists to have a disproportionate impact on the public framing of these technologies generating public perceptions that are not based on good scientific evidence and which have persisted for 20 years (Tait, 2009a).

In the EU, the regulatory system is described as ‘process based’, focusing on the process of genetic modification itself – all technologies developed using this process are treated equally by the regulatory system, regardless of their other properties. In the US and similar jurisdictions on the other hand, regulation is ‘product-based’, focusing on the properties of the resulting product, rather the process used to create it (Tait, 2008). Partly as a result of the regulatory system it has chosen to apply, the US has achieved a globally dominant role in the development of GM-related technologies.

3.6 Critique of the current European regulatory system for GMOs.

A broad range of organisations, several with governance-related remits have criticised the EU regulatory system for deliberate release of GM crops, for its process-based focus, lack of adaptation to evidence of safety of the products currently available, and the political overlay on regulatory decision making (e.g. ACRE, 2007; ACRE, 2013; Baulcombe *et al.*, 2014; Mittra *et al.*, 2014; Tait and Barker, 2011). There appears to be a steady increase in the amount of authoritative criticism of the operation of the EU regulatory system and of the behaviour of some of the NGOs that have been most active in their antagonism to GM crops. The united coalition of advocacy groups (environmental, consumer, third world) that was so influential in framing European citizens’ understanding of GM crops in the 1990s (Tait, 2001) is no longer in existence. Two major pressure groups, the WorldWide Fund and the Royal Society for the Protection of Birds are now no longer campaigning on GM crops or synthetic biology. Friends of the Earth (USA) is actively campaigning against synthetic biology, but Friends of the Earth (UK) has not yet made any commitment. Also Friends of the Earth (UK) has collaborated with the Biotechnology and Biological Sciences Research Council (BBSRC) in supporting a company’s efforts to meet a challenge related to the sustainability of its operations from other NGOs (including Friends of the Earth (US)). Also, rather than the previous advocacy on behalf of poor farmers who were presented as victims in debates about GMOs, there is now considerable evidence of the benefits to poor farmers from these technologies (Cressey, 2013), and developing countries are beginning to develop their own AIB-related research agendas (Falke-Zepeda *et al.*, 2013). There is also a very different media environment compared to the 1990s and early 2000s, with most of the major newspapers and other media outlets taking a much more balanced approach to dealing with news items in the area of AIBs, supported by the Science Media Centre³².

³¹ <http://mgafrica.com/article/2015-08-14-kenya-gmo>; <http://www.biowatch.org.za/list.php?cat=GM%20crops>

³² <http://www.sciencemediacentre.org/>

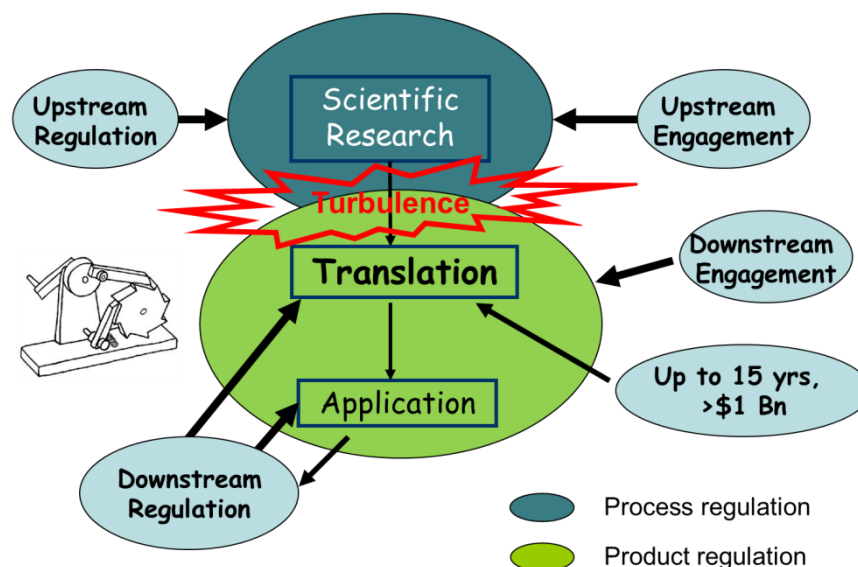
However, from personal experience, including numerous discussions with key players in this area, there is still a prevailing atmosphere of nervousness among scientists and innovators that we could see a return of the vociferous negativity that has surrounded the development of GM crops in Europe, this time directed against synthetic biology and related techniques. Perhaps the greatest dangers here are that displaying this nervousness may (i) generate the feared response and/or (ii) lead to over-compensation such as avoiding research and development in key areas that could be of considerable benefit in future (e.g. avoiding working of organisms designed for deliberate release).

In the EU since the 1980s, two governance related trajectories have been proceeding in different directions and with little or no coordination (Figure 7):

- i. the governance agenda described in Section 1.2 was bringing in a softer, more participative approach to governance including the concepts of upstream engagement and upstream regulation for new technologies in the earliest stages of development; and
- ii. existing product regulatory regimes were changing in the opposite direction, adding new regulatory hurdles in a reactive mode (as in a ratchet) each time a defect emerged in a product or process that had been initially regarded as safe (European Environment Agency (EEA), 2013; Tait and Levidow, 1992).

This 'regulatory ratchet', has seen the cost to companies of meeting the demands of regulatory systems increase to a point where they inhibit the development of innovative technologies by even the largest multinational companies (the costs in Figure 7 (up to 15 years and >\$1 Bn) refer to drug development; the costs for a GM crop in the EU are estimated to be €200 – 500 M, with a currently unlimited timescale (Mittra *et al.*, 2014)). Figure 7 also illustrates how a negative public response to a new technology is most likely to arise at the point where a new technology makes the transition from the conduct of research to consideration of new products or processes to be made available in a market place (in a sense where the legally based regulatory system in operation in the lower portion of the figure meets the participative approach to governance at the earliest stages of research and development).

Figure 7. Life science regulation: upstream governance and the regulatory ratchet.



The report by Baulcombe *et al.* (2014) notes that the commercial release of GM crops is subject to more stringent regulation than conventionally bred plants. It also notes that the “European Academies Science Advisory Council (EASAC) and others have pointed out that there is no rational basis for the current stringent EU regulatory process. There are no reliable data indicating inherent risk for human or animal health, for the environment or from unforeseen effects.”

The current regulatory framework is not seen as conducive to enabling and encouraging small and medium-sized companies that may wish to apply for approval to market GM crops and derived products. Indeed, the associated costs and negative perceptions of the EU approval process have resulted in even large companies developing their new crops elsewhere in the world and withdrawing specific applications for cultivation in the EU marketplace (Tait, 2007).

Box 10. EU Principle of Proportionality and the Principles of Better Regulation:

- Only intervene when necessary.
- Remedies should be appropriate to the risk posed, and costs identified and minimised.
- Policy solutions must be proportionate to the perceived problem or risk and justify the compliance costs imposed – don’t use a sledgehammer to crack a nut.
- All the options for achieving policy objectives must be considered – not just prescriptive regulation. Alternatives may be more effective and cheaper to apply.
- “Think small first”. Regulation can have a disproportionate impact on small businesses.
- EC Directives should be transposed without ‘gold plating’ (the process where a basic EC Directive is given extra strength when incorporated into national laws).
- Enforcement regimes should be proportionate to the risk posed.
- Regulators should consider an empowering and educational, rather than a punitive approach where possible.

There is a new countervailing emphasis in the EU on achieving proportionality in regulatory systems and this could begin to have an impact on the future governance of AIBs. The EU Principle of Proportionality³³, as set out in the Scottish Government ‘Principles of Better Regulation’³⁴, includes the provisions outlined in Box 10.

However a paper from the EU Food and Feed Chain Coalition (2015) points out that none of these principles is currently being applied in the context of the deliberate release of GMOs.

³³ <http://eur-lex.europa.eu/summary/glossary/proportionality.html>

³⁴ <http://www.gov.scot/Topics/Business-Industry/support/better-regulation/5principlesofBetterRegulation>

4. Future governance of AIBs

The above sections have attempted to set out the current governance background for GMOs, and to indicate how they will relate to the governance of AIBs in future. The overall conclusion is that current regulatory systems for GMOs in the EU will provide the basis for future regulation of AIBs and that this could unnecessarily restrict our future capacity to benefit from these technologies. However, it is important also to recognise that there are concerns about our capacity to understand and predict the outcomes of the new more powerful techniques. These perceptions of unpredictability and uncertainty are linked to the promotion of a strong interpretation of the PP that goes considerably beyond the EU recommendations outlined in Section 3.3. Running counter to this tendency to emphasise uncertainty, Nowotny (former president of the European Research Council) has made a powerful case for EU citizens to become more understanding and accommodating of uncertainty in their daily lives (Nowotny, 2016). The challenge for those charged with designing new regulatory systems and with implementing those currently in place is to steer an intelligent course between these countervailing tensions.

This section first describes recent discussions in the EU on the future regulation of AIBs, and also the recent deliberations under the auspices of the UN CBD. Finally it looks at the future regulatory challenges likely to be raised by gene editing and gene drives.

4.1 Future governance of AIBs in the EU

Based on the above analysis, the EU is more likely than some other jurisdictions to err on the side of precaution in its consideration of the future governance and regulation of AIBs and it has begun the process of assessing the regulatory and other infrastructure needed to guide the future development of AIBs. The most significant outcome has been the development of three reports by the Scientific Committees - on Consumer Safety (SCCS), on Emerging and Newly Identified Health Risks (SCENIHR) and on Health and Environmental Risks (SCHER):

- i. Opinion on Synthetic Biology I – Definition³⁵;
- ii. Opinion on Synthetic Biology II – Risk assessment methodologies and safety aspects³⁶;
- iii. Opinion on Synthetic Biology III – Risks to the environment and biodiversity related to synthetic biology and research priorities in the field of synthetic biology³⁷.

The Scientific Committees considered five novel synthetic biology developments: (i) genetic part libraries and methods; (ii) minimal cells and designer chassis; (iii) protocells and artificial cells; (iv) xenobiology³⁸; (v) DNA synthesis and genome editing. Of these developments, only (i) and (v) are likely to be relevant to the concerns of the EAs on a 5-10 year timescale.

In Opinion I, synthetic biology is defined as “the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms”. This definition is described as an operational definition that addresses the needs of risk assessment and is sufficiently broad to include new developments in the field. **The paper also states that synthetic biology “... is currently encompassed within genetic modification as defined in the European Directives 2001/18/EC and 2009/41/EC and**

³⁵ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf

³⁶ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_048.pdf

³⁷ http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_050.pdf

³⁸ Xenobiology: biological systems based on forms of DNA, and manufacture of amino acids and proteins, that are not found in nature – an expanded genetic code.

will remain so in the foreseeable future.” The opinion emphasises the difficulty of defining accurately the relationship between GM and synthetic biology and has produced an additional list of criteria covering “... any organism, system, material, product or application resulting from the introduction, assembly or alteration of the genetic material in a living organism”.

Opinion II focuses on the implications of likely developments in synthetic biology on human and animal health and the environment and on whether existing risk assessment practices for GMOs are adequate. It concludes that within the scope of current GMO regulations, risk assessment is challenging because of the lack of comparators and the increasing numbers of genetic modifications and engineered organisms. The areas described as most challenging are: (i) integration of protocells into living organisms and future developments of autonomous protocells; (ii) new xenobiological variants; (iii) DNA synthesis and direct genome editing of zygotes; and (iv) new multiplexed genetic modifications involving large scale DNA synthesis and/or highly parallel genome editing. Only the last of these developments is likely to be relevant to the EAs on a 5-10 year timescale. Current risk assessment methodologies are described as appropriate, with the addition of some safeguards to ensure continued safety protection while enabling scientific and technological advances. It also considers the use of ‘safety locks’³⁹, concluding that no single technology in this area solves all biosafety risks and many new approaches will be necessary, and recommending development of a strategy for devising new forms of biological containment and combining different forms of containment.

Opinion III addresses specific risks of synthetic biology to the environment, partly in the context of the UN CBD Decision XI/11⁴⁰ that began the UN process “Noting, based on the precautionary approach, the need to consider the potential positive and negative impacts of components, organisms and products resulting from synthetic biology techniques on the conservation and sustainable use of biodiversity” (see Section 4.2). This EU opinion appears biased in that it repeats, from CBD discussions, a list of negative impacts on land use that could be initiated by developments in synthetic biology, but does not mention the counterbalancing potential positive land use impacts that are also included in the CBD discussions (see Section 3.1 and 4.2). The risk factors identified are similar to those relevant to GMOs (accidental release, persistence in the environment, invasion or disruption of food webs, vertical or horizontal gene transfer). Where new threats are identified the opinion repeats the recommendations of Opinion II on the use of ‘safety locks’ or ‘firewalls’ and under the heading of ‘genetic parts’ it recommends supporting research on interactions between modified and natural parts, development of new tools to predict emergent properties of organisms and potential failure modes, development of guidelines for risk assessors on the evaluation of emergent properties of engineered systems, and using GMOs with a proven safety record as comparators for risk assessment. Additional recommendations cover research requirements for a range of potential impacts on biodiversity and conservation.

The recommendations of these reports, the last of which was published in Dec. 2015, have yet to be implemented but the statement above from Opinion I makes it clear that synthetic biology and its products are currently included under the EU regulatory system for GMOs.

³⁹ ‘Safety locks’ provide a form of biological containment and include techniques that have been referred to in the context of GMOs as ‘genetic use restriction technologies’ (GURTS) and (pejoratively) as ‘terminator’ technology. Synthetic biology has the capability to greatly increase the effectiveness of such techniques.

⁴⁰ <https://www.cbd.int/doc/decisions/cop-11/cop-11-dec-11-en.pdf>

Synthetic biology and other AIBs are being targeted as campaigning issues by some of the NGOs that were influential in the anti GM campaigns that began in the 1990s, among the most prominent being the Canadian group 'etc'⁴¹ and Friends of the Earth (USA)⁴², alongside a wide range of smaller campaigning bodies. These groups are actively engaged in attempting to influence future regulatory systems and policies for AIB development on the basis of an absolutist rather than a relativist approach to risk that ignores benefits and amplifies uncertainty (Tait, 2014). Included in their campaigning documents are suggestions that contained use of GMOs, as in industrial biotechnology, should no longer be treated as a less hazardous process than deliberate release and should be regulated through the EU Deliberate Release Directive. As in other areas of risk and uncertainty amplification, the case is based on vague speculation with no plausible scenarios proposed based on realistic future developments by companies.

4.2 Future UN governance of AIBs

The UN CBD Decision XI/II referred to above began a lengthy process of consultation and meetings on whether synthetic biology is a new and emerging issue under the CBD, in which case the CBD would be able to develop additional rules governing its use. These developments included a process of global consultation among a broad range of experts on seven key questions related to the relationship between synthetic biology and biodiversity and its future governance. The overall process and outcomes are summarised in the report produced by the Ad Hoc Technical Expert Group on Synthetic Biology on 7 October 2015⁴³, including the agreed operational definition of synthetic biology (very similar to the EU definition) for this process:

“Synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems.”

The open-ended on-line discussion which was part of this process took place over the summer of 2015 covering seven topics related to the impact of synthetic biology on biological diversity and the full set of responses can be seen on the CBD website⁴⁴. The outcomes of these on-line discussions are summarised in a report of the Ad Hoc Technical Expert Group⁴⁵ which also noted that 235 experts were nominated to participate in the forum and a total of 402 interventions were made. Up until 2015, the voices of the scientific and industry communities had been largely silent in debates surrounding the activities of the CBD, compared to the very strong representation from environmental advocacy groups (Kuiken, 2015), but the contributions to this latest forum were much more balanced across a range of stakeholder perspectives and interest-based and value-based positions (See Table 2, Section 3.4). However, the summary report of the discussions did not reflect the full range of opinions expressed in these contributions⁴⁶, underplaying those from scientists and industry and also from numerous policy makers and regulators. As a result of this broader stakeholder representation in the discussions it has been more difficult than in the past to reach agreed decisions on synthetic biology related issues in the

⁴¹ <http://www.etcgroup.org/>

⁴² <http://www.foe.org/about-us/friends-of-the-earth-international>

⁴³ <https://www.cbd.int/doc/meetings/synbio/synbioahteg-2015-01/official/synbioahteg-2015-01-03-en.pdf>

⁴⁴ <https://bch.cbd.int/synbio/open-ended/discussion.shtml>

⁴⁵ <https://www.cbd.int/doc/meetings/synbio/synbioahteg-2015-01/official/synbioahteg-2015-01-02-en.pdf>

⁴⁶ http://www.innogen.ac.uk/downloads/SBLC-REsponse-CBD-Notification_30Jan16.pdf

relevant committees and it is not yet clear whether the open-ended forum will have resolved these differences.

4.3 The special case of gene editing

The gene editing techniques described in Box 1 are very powerful: they can greatly speed up research and therefore the productivity of the researchers, enabling the products to enter into industrial production more rapidly, provided industry can see viable commercial opportunities based on them. As noted above, in the EU at least, it is the intention that synthetic biology will be regulated through the same system as currently applies to GMOs. However, in the case of gene editing, discussion has revolved around whether or not gene editing should be regarded as a development of synthetic biology, one of the challenges being that, in some cases, it will be impossible to tell what method was used to produce a new plant variety (BBSRC, 2014; Postnote, 2015).

The BBSRC (2014) report describes new benefits arising from gene drives but does not refer to any new hazards that would not be controlled through existing regulatory systems. However they do emphasise the need for proactive discussion with a broad range of stakeholders to provide the context within which these technologies should be evaluated. They also call for a new trait-based, rather than process-based, approach to regulation involving evidence-based risk assessment, to deliver proportionality in EU regulatory systems.

Despite some suggestions to the contrary, the EU definition of synthetic biology does seem to cover gene editing although delay in deciding if GM regulations apply to gene editing is claimed to be affecting important scientific research (Abbott, 2015). Also, experience with GMOs in the EU suggests that having made the decision to regulate this technology as a GMO will not necessarily facilitate future innovative developments.

In the USA on the other hand some products of gene editing are now entering commercial development without being regulated:

- US regulators have ruled that several products of gene editing do not fall under the remit of their regulatory system (Editorial, 2016);
- In a case described as the 'unregulation' of GM crops (Grens, 2015) an apple variety (Arctic apple) designed not to brown on exposure to air has been deemed not to require regulation as a GMO; and
- The US Department of Agriculture has decided not to regulate a mushroom genetically edited using CRISPR-Cas9 to resist browning [http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754?WT.ec_id=NEWSDAILY-20160415].

The common feature in these US examples is that these products do not contain foreign DNA from 'plant pests' such as viruses or bacteria, the criterion that would lead to their capture by the US regulatory system, although there may still be a voluntary review by the US Food and Drug Administration to check on safety for human consumption. These and other anomalies arising in the US product-based regulatory approach are leading to reconsideration of the current regulatory system for AIBs in light of these new developments (Ledford, 2016).

The techniques covered under the heading of gene editing will require more varied and nuanced consideration than would be possible under the general heading of 'GMO' and we may be only at the beginning of a new round of debate and dialogue on these issues. There are no apparent threats to biological diversity or to other aspects of environmental safety from gene editing

technologies that would trigger the application of the PP, as specified in the EU guidance (Box 7). However, it may be wise to conduct some formal scenario analyses to explore more fully these assumptions of safety.

4.4 Issues arising from gene drive technologies

One of the AIB techniques described in Box 1, the gene drive, currently in early stages of development, will require special consideration on how it should be governed (Oye *et al.*, 2014). The key difference between a gene drive and other AIBs is that the genetic trait is built into its DNA in a way that ensures that it is passed down through generations and can spread quickly and permanently through an entire population. If the trait is deleterious or lethal it can wipe out the target population but it is only effective in species that reproduce sexually and do so rapidly. Potentially attractive applications include wiping out malaria-bearing mosquitoes in a region or eliminating alien invasive rodent species from an island ecosystem where they are having negative impacts on biodiversity. (US National Academies of Sciences, Engineering, and Medicine, 2016)

Gene drives will not be governable under current GMO regulations, all of which currently require demonstration that, either an organism will not spread in the natural environment or that it will not cause any fundamental change in ecosystems if it does so. It is also important to note that gene drives, being a potentially one-off development with no commercially attractive business model, will most likely be developed by governments, or at least under close government supervision, making their governance more controllable, particularly in the early stages of development. However, from the point of view of the EAs, there are not as yet any likely applications of gene drives within their territory.

The Dutch National Institute for Public Health and the Environment has produced a useful policy report on gene drives (Westra *et al.*, 2016), recommending:

- Adapting current legislation so that it is no longer possible to inadvertently create a gene drive;
- That authorisation should only be granted if sufficient information is available to answer all questions in the risk assessment to ensure the safe use of organisms with a gene drive and provide an opportunity to gain knowledge about the way gene drives work and their impact; and
- That an international approach should be sought since this may concern organisms and potential effects on human health and the environment that could spread across national borders.

Also, the U.S. National Academy of Sciences has published recommendations for responsible practices on gene drive research in non-human species (US National Academies of Sciences, Engineering, and Medicine, 2016).

5. Conclusions and recommendations: a proportionate and adaptive approach to the governance of AIBs

The objectives of this analysis are:

- i. To assess the scale and likely impact of AIBs on the ability of the UK and ROI to regulate the relevant sectors in future;
- ii. To advise on the development of a proportionate approach to regulation of these sectors, given the potential future timeline of developments and commercial adoption, and given that the capacity of the sectors to deliver the expected impact, positive or negative, will depend on the regulatory approach adopted;
- iii. To identify and explain (with evidence) any current and potential future risks that may not be covered by the proposed regulatory approaches, including both contained use and deliberate release; and
- iv. To stimulate and guide future discussions among the UK and Republic of Ireland (ROI) EAs and also AIB-related practitioners and the wider public.

The analysis in Sections 2 – 4 is based on research and experience since the 1980s on the development of GMOs and other AIBs, covering objectives (i) – (iii). To summarise the key points in the analysis.

- i. AIBs could have major contributions to the bioeconomy and the circular economy, in the UK and globally.
- ii. On a 5-10 year timescale, the innovations arising from AIBs are expected to be incremental rather than disruptive for the industry sectors involved.
- iii. This means that the expected innovations are unlikely to raise additional public concerns, beyond those already raised by some applications of GMOs, or to lead to a need for additional regulatory oversight, except among advocacy groups that engage with the technology from an ‘in principle’, ideological perspective.
- iv. The regulatory systems to be applied to AIBs in the EU will be those currently in place for GMOs in contained use and deliberate release.
- v. A major threat to achieving some of the expected benefits from these AIBs in non-contained uses arises from the current EU regulatory system that is widely seen as not being sufficiently proportionate or adaptive to available knowledge and evidence of their benefits and hazards.
- vi. Among some regulators, policy makers and company managers, there is a persistent, probably unjustified, impression that a majority of the EU population is ideologically opposed to GM crops and a fear that this will be extended to AIBs.
- vii. Several prominent environmental advocacy groups and a large number of much smaller groups are attempting to raise concerns, so far unsupported by realistic scenarios, about the contained use of AIBs and the hazards to the environment in the event of an escape from containment.
- viii. There is insufficient understanding among policy makers and regulators of how to interpret data from stakeholder engagement and opinion polls, and how to conduct future engagement in this context with its history of misunderstandings and misinterpretation.

Section 5 focuses on objective (iv), considering on what basis, how, with whom, and when to stimulate further discussion to inform the work of the EAs. Section 5.1 describes the background to the proposals and recommendations introduced in Sections 5.2 – 5.4. Section 5.2 describes an approach to working within the changing decision making environment for policy makers and regulators, involving new or more insistent demands to ensure that regulations are proportionate and adaptive to the properties of innovative technologies and that they do not unnecessarily inhibit innovation. Engagement and dialogue with citizens and stakeholders is an important component of innovation governance and will contribute to future discussions and policy decisions on AIBs. It could usefully build on improved understanding of the complex motivations and interactions within and between societal and professional groups and Section 5.3 offers guidelines relevant to this process. Section 5.4 describes an approach that could usefully be adopted as a basis for integrating understandings and actions required to manage the governance of AIBs in the next 5 – 10 years. Section 5.5 makes recommendations for the EAs in delivering such a strategy.

5.1 The potential impacts of AIB-related innovation

AIBs have the potential to exert a major impact on the global bioeconomy, to enable us to reduce our ecological footprint and to “tread more lightly on the planet” (Wackernagel and Rees, 1996). They are a key component of future plans to build a circular economy, as committed to by all the governments of the countries and regions involved in ShARE (see Section 2.2) and there is significant government investment in a broad range of initiatives designed to support this outcome.

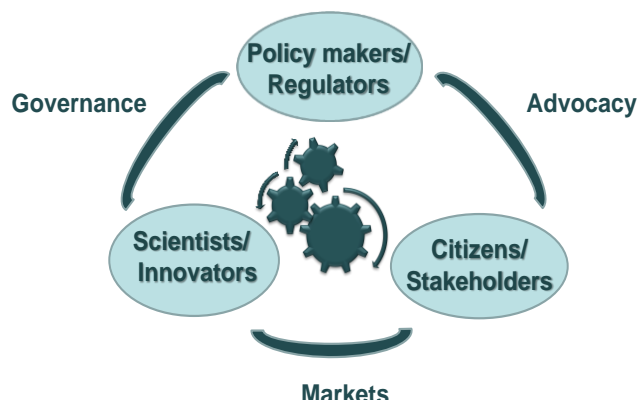
Section 2.1 considered the extent to which the AIBs likely to be developed in the next 5 – 10 years could have disruptive impacts on product types or lead to radical restructuring of industry sectors, and concluded that innovation on this timescale is likely to be mainly incremental, with some disruption of manufacturing processes in contained use of AIBs. The companies likely to take a lead in delivering these expected benefits to the bioeconomy will be the multinational industrial biotechnology, pharmaceutical, agro-biotechnology, seed and food companies operating in today’s chemicals and fossil fuel based sectors.

An important constraint on the economic potential of AIBs will be that, given the scale of existing regulatory hurdles (Section 2.2), small and medium-sized companies will not be able to innovate independently of the strategies of the major multinational companies (Tait, 2007). There are many currently feasible developments that could be commercially attractive to these smaller, younger companies and the ability of the bioeconomy to contribute to a circular economy will be limited if they are not able to address the local needs and opportunities that could make major differences to ecological footprints. An additional factor, impossible to quantify, is that smart innovators will avoid altogether undertaking the necessary research and development to deliver these types of benefit, again to the potential detriment of the circular economy.

The Innogen Institute’s research programme⁴⁷ (Figure 8) has demonstrated the extent to which the regulatory systems in place for life science based industries, in addition to ensuring the safety, quality and efficacy of products and processes, will determine:

⁴⁷ <http://www.innogen.ac.uk/downloads/Innogen-Institute-Research-Outline.pdf>

Figure 8. Innogen Institute research framework: key actors and their impacts



- the innovation strategies of companies,
- the extent to which the disruptive innovations that could respond to currently-unmet societal needs are able to be developed,
- the innovativeness of industry sectors,
- the geographic location of companies,
- the scale of operations of the companies involved, and
- ultimately, the relative competitive advantage of the regions and nations of the world.

For AIBs the regulatory systems in operation for a sector (i.e. the governance relationship between policy makers/regulators and scientists/innovators in Figure 8) could be the primary factor in enabling or constraining the emergence of a circular economy. More adaptive and proportionate governance of innovative technologies is increasingly seen to be the answer to such problems, along with the introduction of an ‘innovation imperative’ (OECD 2015). However, there is little guidance for policy makers and regulators on how this should be achieved, and this report attempts to fill that gap.

The citizen/stakeholder perspective included in Figure 8 is also an important component of the approach to governance introduced in Section 1.2 and elaborated in the context of AIBs in Section 3.4. Without the markets that citizens and stakeholders will provide, there will be no commercially viable innovation and, as has been clearly demonstrated through the EU regulatory system for GMOs, their advocacy influence on policy makers and regulators can have an equally decisive role in determining what technologies are able to be developed. Again there has been little critical guidance on how to manage these interactions more constructively than has been the case to date.

5.2 Supporting decision making on proportionate and adaptive regulation of AIBs.

Regulators and policy makers are increasingly tasked, beyond their roles in maintaining safety, quality and efficacy in products and processes, with ensuring that regulations are proportionate to the expected risks from novel technologies and are also adaptive to the need to facilitate the development of useful innovations (Tait and Banda, 2016a, 2016b). Our conclusion that existing regulatory systems for GMOs will be adopted and will be adequate to deal with the expected developments of AIBs is supported by the UN on-line consultation undertaken in 2015 (Section 4.2) where a very large body of opinion across researchers, innovators, policy makers and regulators considered that existing regulatory approaches, applied on a case-by-case basis as in current practice, will be adequate to deal with these new technologies and their potential impacts on biodiversity.

Where contributors to the UN on-line consultation (Section 4.2) were concerned about the hazards arising from synthetic biology, these were couched in general terms. None of the statements about future risks provided the kind of detailed scenario that would be needed to meet the criteria for adoption of the PP according to the EC Guidelines (Box 7). Speculation based

on greater complexity, greater volume of activity, or greater power in the techniques available, without further elaboration, would not be sufficient to stimulate additional regulatory action. Indeed, experience in other industry sectors, such as motor vehicles, aircraft, or pharmaceuticals, suggests that greater power and complexity and greater volume of activity is associated with improved safety.

The choice to regulate next generation AIBs through the system in place for GMOs, can be seen as potentially providing reassurance to those concerned about potential environmental hazards. However, meeting the requirements for regulatory approaches also to be more proportionate

Box 11 Adaptive Governance of Innovative Technologies

A more adaptive risk governance approach for AIBs would aim to be:

- *enabling* of innovation,
- *minimising* risk to people and the environment, and
- *balancing* the interests and values of all relevant stakeholders.

It would provide for trade-offs between these factors and support smarter regulatory approaches that balance potential societal and economic benefits and potential risks, particularly where both are uncertain in the early stages of technology development.

and adaptive to the needs of innovative technologies (Section 3.6) could be seen as a requirement to go beyond the *status quo* and consider how the current systems could be made more adaptive based on evidence of the lack of environmental hazards arising from the GMOs in use throughout the world today. Given that EU regulations on deliberate release of GMOs are increasingly being criticised by well-informed authoritative sources for lack of proportionality and adaptation it will be important for regulators and policy makers to learn from past experience of the safe and environmentally beneficial development of GM crops, including experience beyond the boundaries of the EU.

Box 11 summarises the key requirements of an adaptive approach to the governance of innovative technologies being developed by the Innogen Institute (Lowrie and Tait, 2011; Tait and Barker, 2011) and Section 5.4 describes how this could be implemented through an approach being developed in collaboration with the British Standards Institution (BSI).

5.3 Constructive stakeholder engagement

Stakeholder engagement is an important component of the governance process, as described in Section 1.2 and the problems experienced in the conduct of stakeholder engagement in the EU, outlined in Section 3.4 are still to some extent unresolved. There is a continuing perception in policy circles of the desirability of upstream engagement at as early a stage as possible in the development of a novel technology (Figure 7) but little recognition of the difficulties and biases that can be introduced through such an approach (Table 3) (Tait and Barker, 2011).

Table 3. Problems in applying upstream engagement to innovative technologies

Group think	The views of small groups will be easily swayed by participants with strong opinions or by those leading the engagement.
Issue framing	Given our ignorance about the future, engagement can be a process of fictitiously framing new science and technology in the minds of the public.
Recruitment bias	It is difficult to persuade uncommitted citizens to participate in hypothetical discussions about science and innovation a long time in the future – those who engage are likely to have a specific agenda.
Conflict	Where there is polarisation of views, engagement can lead to increased levels of conflict.
Engagement focus	Some topics (e.g. synthetic biology, nanotechnology) are too broad and multi-faceted to allow meaningful engagement.
Engagement fatigue	There will be insufficient time and resources to engage on every relevant issue and people will become cynical about the process
Labile public opinion	People who do not already have strong opinions will change their minds over quite short timescales, much more so over 5-10 years.

There is a need for better understanding of these and other pitfalls and for guidance on how to avoid them. The recommendations in Box 12, part of the Innogen Institute guidance on Constructive Stakeholder Engagement (Tait and Barker, 2011; Tait, 2009), are relevant to the questions raised above in relation to objective (iv) - on what basis, how, with whom, and when to stimulate discussion to inform the work of the EAs. They are seen as a counter-balance to the EU approach that has seen the governance of GMOs and related technologies become increasingly dominated by the values of a vociferous minority⁴⁸.

⁴⁸ http://www.innogen.ac.uk/downloads/ConsultationResponse_HOC_EURegulationOfLifeSciences.pdf

Box 12. Constructive Stakeholder Engagement

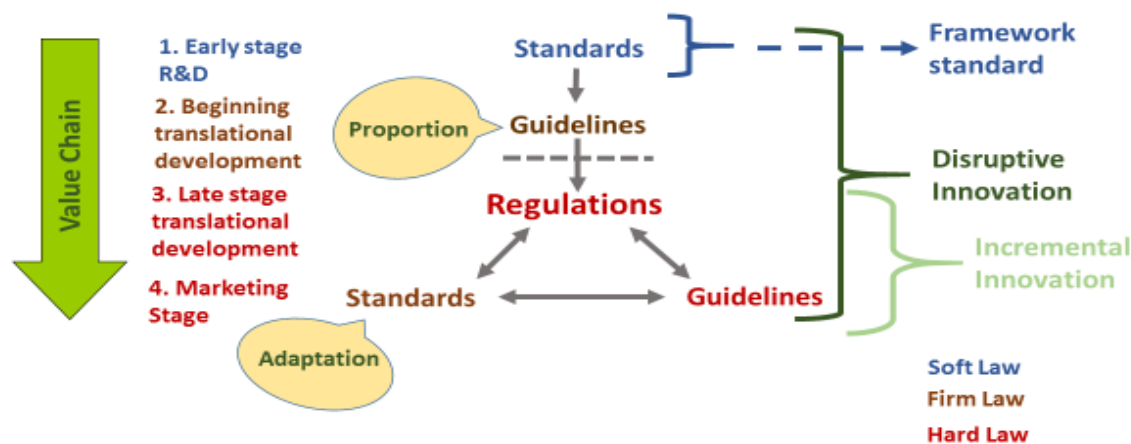
- Engage about innovation and regulatory processes, as well as science and technology.
- Consider benefits of the technology and balance against costs and risks.
- Develop standards for engagement including standards for the quality of evidence on which decisions are based.
- In a plural democracy, maintain choice as far as possible.
- Have an open discussion, including the full range of relevant opinions (general public/citizens, scientists, industry, users of the technology, consumers).
- No single perspective should dominate other opinions.
- Manage expectations – it is unlikely that all stakeholder views can be accommodated.
- Careful timing – too early and its value will be undermined by the level of uncertainty around the nature of future developments; too late and stakeholder opinions and political positions may have become entrenched, leading to the risk of further polarisation and making accommodation more difficult to achieve.

5.4 Combining proportionate, adaptive governance and constructive stakeholder engagement

The Innogen Institute report to the BSI⁴⁹ (Tait and Banda, 2016 a, b) considers how to achieve proportionate, adaptive governance alongside a more constructive approach to stakeholder engagement, and is relevant to AIBs and the remit of the EAs. The report develops a governance framework (Figure 9), applicable across a range of advanced innovative technologies with widely differing histories and experiences of regulation, including synthetic biology/industrial biotechnology.

The green arrow on the left of Figure 9 represents the value chain⁵⁰ for an AIB, alongside a much-simplified representation of the stages of development, from early stage research and development (R&D) through early and late translational stages to marketing. The central set of relationships in Figure 9 shows how, across these different developmental stages, the components of the regulatory system (standards, guidelines and regulations) will play different roles involving ‘soft’, ‘firm’ and ‘hard’ law⁵¹ at different stages of development. Where regulation of human and environmental hazards is involved, the governance system will move closer to hard law as products near market-readiness.

Figure 9. Framework combining proportionate and adaptive governance of innovative technologies with a constructive approach to stakeholder engagement (British Standards Institution Report (Tait and Banda (2016b))



⁴⁹ Numerous types of standards are used by industry for a broad range of purposes. The BSI report focuses on the relatively orderly, authoritative and widely applicable types of standard developed by national standards bodies, such as the BSI, and international standards organisations, comparing the roles and impacts of such standards to those of regulations and the guidelines developed by regulators in support of regulation, and proposing greater integration of standards within a governance process to deliver proportionality and integration.

⁵⁰ The following definition of a ‘value chain’ (Mastroeni *et al.*, 2014) adapts its use to life science sectors: “ ‘Value chain’ describes the full range of activities required to bring a product from conception to end use and beyond, including design, production, marketing, distribution and support to the final consumer. Depending on the nature of the opportunity and the complexity of the route to exploiting it, the value chain will encompass a number of firms with different business models operating in sequence or in parallel.”

⁵¹ Hard law has government based legislative enforcement to ensure compliance; firm law is backed up by some form of legislative authority but may not be legally enforced; soft law has no formal legislative authority and relies on codes of conduct reinforced by peer pressure or (for some standards) market related mechanisms.

The BSI report (Tait and Banda, 2016 a, b) considers how an enhanced, more integrated role for standards in governance processes could deliver the required proportionality and adaptation as illustrated in this central set of relationships. The right hand side of Figure 9 draws attention to the different sets of demands raised by disruptive and incremental innovation, and also the potential role of a Framework Standard in stakeholder engagement (Section 5.4.1).

To summarise how proportionality could be achieved for a *disruptive* AIB-related innovation for which there is no existing regulatory precedent, reading from top to bottom of the diagram, the governance process should:

- i. In the early R&D stage (Stage 1) of developing the technology, focus on consensus standards devised in collaboration with companies and scientists with expertise in the area to consider what the potential hazards might be, how they could be addressed and whether there are any relevant existing regulatory systems;
- ii. As experience is gained and the likely future nature of the emerging innovative products and processes becomes clarified (Stage 2), adapt these standards and begin to formalise them as guidelines that could then form the basis of a future regulatory system (this stage involving companies and scientists and also regulators and policy makers);
- iii. Once the nature of the innovation and its future potential have been clarified, again in an open democratic process involving all interested stakeholders, develop legally binding regulations, couched in general terms relating to the desired outcome of the regulation; and
- iv. At the marketing stage (Stage 4), again in an open democratic process involving all interested stakeholders, devise standards and guidelines to support compliance by those engaged in developing the new technology.

The innovations arising from AIBs on a 5 – 10 year timescale are likely to be *incremental* in nature and to be regulated through the existing GMO regulatory systems which, in the EU, involve legally-based regulations having the status of ‘hard law’ (Section 3.5). For AIBs, as incremental innovations, from stage (iii) above the concern is mainly how to *adapt* these regulations and guidelines to make them more *proportionate* to the expected hazards and benefits. The BSI Governance Framework proposes that development and adoption of standards, working alongside existing regulatory guidelines or replacing them in some cases, with the involvement of a broad range of stakeholders could play an important role in enabling such adaptation.

The process outlined above for Stages (i) – (iv) of the innovation process intentionally implies a different approach to stakeholder engagement in stages (i) and (ii) where the nature of products and their potential benefits and hazards are ill-defined and mutable. At Stages (iii) and (iv) these properties will have been sufficiently defined to allow an informed consideration of relevant issues by all stakeholders. The next section (5.4.1) describes how a Framework Standard could guide overall stakeholder dialogue and engagement, including at Stages (i) and (ii), as a contribution to future more adaptive and proportionate governance of AIBs.

5.4.1 The potential of a Framework Standard

Figure 9 includes the role of a Framework Standard for the responsible development of innovative technologies (Steedman, 2013) to resolve some of the difficulties with governance and stakeholder engagement that have been experienced in the EU in the context for AIBs (Section 3.4). A Framework Standard is a voluntary consensus standard, similar to the Environmental Management Standard, developed by BSI and now administered through the International

Standards Organisation as ISO 14001⁵². For a disruptive innovation, its development could begin at the earliest stages of R&D, whereas for an incremental innovation it could be introduced at any point along the innovation value chain.

An important part of the value of such a Framework Standard would be in enabling a more *constructive* approach to stakeholder engagement, at all stages along an innovation pathway, answering the questions on the timing, basis and constituency for engagement initiatives (Section 5.3). A well-executed stakeholder engagement can cost up to £100K and in the early R&D stage of development of an AIB it is not appropriate (because of lack of scientific evidence) or valid (given the issues raised in Table 3) to conduct stakeholder engagement for specific innovations. However, in the later stages of an innovation pathway (Stages 3 and 4 in Figure 9) evidence will be available on the technical and commercial feasibility of specific innovations and their expected properties and it would be appropriate to involve all interested citizens in considering how the technology should be governed.

The value of a Framework Standard in the context of AIBs would lie:

- i. In guiding the type of dialogue undertaken at different stages of an innovation pathway, bringing together relevant stakeholders at each stage, and including standards for the conduct of a dialogue similar to those described in Box 11, taking into account the timing and other pitfalls outlined in Table 3; and
- ii. In the potential involvement of all stakeholders at Stage 4, in monitoring and ensuring adherence to the requirements of standards introduced to ensure implementation of regulations and guidelines.

⁵² <http://www.bsigroup.com/en-GB/iso-14001-environmental-management/ISO-14001-revision-new/>

5.5 Recommendations: potential roles for the EAs in future governance of AIBs

The EAs, in fulfilling their roles as outlined in Section 1.3, occupy an important position at the interface between the regulatory systems and those involved in implementing them, both in ensuring environmental protection and sustainable economic growth and in alerting governments to future hazards and regulatory requirements. Much could be gained from a more strategic approach to the governance of AIBs that takes account of the factors outlined in this report and the EAs could play a prominent role in such a strategy.

Through the future discussions referred to in Objective (iv), the EAs could begin the process of informing themselves and those with whom they engage about their national and regional needs and concerns, covering the following aspects:

- i. The potential contributions of AIBs within their territory to the circular economy and the bioeconomy including –
 - The availability and carrying capacity of natural resources and/or by-products from current production processes as feedstock for AIB-related processes;
 - The opportunities for industries to contribute more effectively to a circular economy;
 - Companies' plans for future AIB-related developments and how they could contribute to a national agenda for a circular economy.
- ii. Engaging across the regulatory interface to influence future governance-related developments for AIBs –
 - Based on a good appreciation of the likely future developments in their areas of authority and their potential impacts, positive and/or negative, on the regional environment (derived from (i) above);
 - To ensure that the governance and regulatory systems deployed at national and regional levels are proportionate and adaptive and able to minimise any hazards arising from AIBs in future while maximising the benefits.
- iii. Developing an on-going dialogue with citizens and other relevant stakeholders –
 - To support better understanding of their needs and desires and of the underlying motivations;
 - To enable more effective evidence-based communication on potential hazards and benefits of existing and new AIBs;
 - To avoid unnecessary polarisation of opinion in the future management of AIB development.

The frameworks and guidelines described in Sections 5.2 – 5.4 could provide a basis for the conduct of these discussions and could also contribute to the development of future strategies for the governance of AIBs in a manner that enables them to deliver their full potential to the bioeconomy and the circular economy, and also to the improvement of the natural environment.

References

- Abbott, A. (2015) Europe's genetically edited plants stuck in legal limbo. *Nature*, 528, 319-320.
- ACRE (2007) *Managing the Footprint of Agriculture: Towards a Comparative Assessment of Risks and Benefits for Novel Agricultural Systems*. Report of the ACRE Subgroup on wider issues raised by the farm scale evaluations of herbicide tolerant GM crops.
<http://webarchive.nationalarchives.gov.uk/20080727101330/http://www.defra.gov.uk/environment/acre/fsewiderissues/pdf/acre-wi-final.pdf>
- ACRE (2013). *Genetically modified organisms: the case for new regulations*.
<https://www.gov.uk/government/publications/genetically-modified-organisms-the-case-for-new-regulations>
- Baulcombe, D., Dunwell, J., Jones, J., Pickett, J. and Puigdomenach, P. (2014). *GM Science Update: a report to the Council for Science and Technology*.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/292174/cst-14-634a-gm-science-update.pdf
- BBSRC (2014) *New techniques for genetic crop improvement*. Position Statement.
[<http://www.bbsrc.ac.uk/documents/genetic-crop-improvement-position-statement-pdf/>]
- Buhk, H.-J. (2014) Synthetic biology and its regulation in the European Union. *New Biotechnology*, 39(6), 528-531.
- Chamberlain, L., Jansin, E. and Raksit, A. (undated) *Wales and the circular economy: favourable system conditions and economic opportunities*. Ellen Macarthur Foundation for the Waste and Resources Action Programme (WRAP) and the Welsh Government.
[http://www.wrap.org.uk/sites/files/wrap/Wales_and_the_Circular_Economy_Final_Report.pdf]
- Chambers, G., Dreisin, A. and Pragnell, M. (2015) *The British bioeconomy: an assessment of the impact of the bioeconomy on the UK economy*. Capital Economics, Report to BBSRC.
(<http://www.bbsrc.ac.uk/documents/capital-economics-british-bioeconomy-report-11-june-2015/>)
- Commission of the European Communities (2000) *Communication from the Commission on the Precautionary Principle*. Brussels 2.2.2000 COM(2000)1 final. [<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52000DC0001&from=EN>]
- Cressey, D. (2013) A New Breed. *Nature*, 497, 27-29.
- Editorial (2016) Breeding controls: scientists must help to inform regulators wrestling with how to handle the next generation of genetically engineered crops, *Nature*, 532, 147; (14 April 2016)
doi:10.1038/532147a
- EEA (2013) *Late Lessons from Early Warnings: science, precaution, innovation*. EEA Report, 1.2013. <http://www.eea.europa.eu/publications/late-lessons-2>
- EPA (2014) *Towards a resource efficient Ireland: a national strategy to 2020*.
[<http://www.epa.ie/pubs/reports/waste/prevention/TowardsAResourceEfficientIreland.pdf>]
- EU Food and Feed Chain Coalition (2015) *Position paper for a functioning evidence-based EU policy on GMOs*. Brussels, 28 May, 2015. [<http://www.europabio.org/EU-Food-Feed-Chain-Coalition-Position-for-functioning-evidence-based-EU-policy-GMOs>]

- Evans, J., Wood, G. and Miller, A. (2006) The risk assessment-policy gap: an example from the UK contaminated land regime. *Environment International*, 32, 1066-1071.
- Falke-Zepeda, J.B., Guillaume, P.G. and Idah, S.-N. (2013) *GM crops in Africa: economic and policy lessons from countries south of the Saharah*. Washington DC: International Food Policy Research Institute. [<https://www.ifpri.org/publication/genetically-modified-crops-africa>]
- Gaskell, G. *et al.*, (2006) *Europeans and biotechnology (2005): Patterns and trends. Final Report on Eurobarometer 64.3*. A Report to the European Commission's Directorate General for Research. [http://ec.europa.eu/public_opinion/archives/ebs/ebs_244b_en.pdf]
- Grens, K. (2015) The unregulation of biotech crops. *The Scientist*. [<http://www.the-scientist.com/?articles.view/articleNo/44624/title/The-Unregulation-of-Biotech-Crops/>]
- HoC Environmental Audit Committee (2014) *Growing a circular economy: ending the throw-away society*. Third Report of Session 2014-15. <http://www.publications.parliament.uk/pa/cm201415/cmselect/cmenvaud/214/214.pdf>
- HoC Science and Technology Committee (2013). *Bridging the valley of death: improving the commercialisation of research*. Eighth Report of Session 2012-13; HC 348 <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348.pdf>
- Ipsos Mori (2014) *Public Attitudes to Science 2014*. <https://www.ipsos-mori.com/Assets/Docs/Polls/pas-2014-main-report.pdf>
- IRGC (2009) *Risk Governance Deficits: an analysis and illustration of the most common deficits in risk governance*. Geneva: IRGC www.irgc.org.
- Jones, JDG *et al.* (2014) Elevating crop disease resistance with cloned genes. *Phil. Trans. R. Soc. B* 369: 20130087. <http://dx.doi.org/10.1098/rstb.2013.0087>
- Klümper W and Qaim M (2014) A Meta-Analysis of the Impacts of Genetically Modified Crops. *PLoS ONE* 9(11): e111629. doi:10.1371/journal.pone.0111629.
- Kuiken, T. (2015) Shaping the future of synthetic biology.
- Kwok, R. (2010) Five hard truths for synthetic biology. *Nature*, 463, 288-290.
- Lacroix R, McKemey AR, Raduan N, Kwee Wee L, Hong Ming W, *et al.* (2012) Open Field Release of Genetically Engineered Sterile Male *Aedes aegypti* in Malaysia. *PLoS ONE* 7(8): e42771. doi: 10.1371/journal.pone.0042771
- Ledford, H. (2016) Gene –editing surges as US rethinks regulations. *Nature News* [<http://www.nature.com/news/gene-editing-surges-as-us-rethinks-regulations-1.19724>]
- Lowrie, H and Tait, J. (2011) *Guidelines for Appropriate Risk Governance of Synthetic Biology*. International Risk Governance Council Policy Brief <http://www.genomicsnetwork.ac.uk/innogen/publications/innogenpolicybriefs/title,25986,en.html>
- Mastroeni, M., Mittra, J. and Tait, J. (2012) *Methodology for the Analysis of Life Science Innovation Systems (ALSIS) and its Application to Three Case Studies*. TSB Regenerative Medicine Programme: Value Systems and Business Models. REALISE Project. Innogen Centre Report to Technology Strategy Board. 29th May, 2012. <http://www.innogen.ac.uk/reports/490>
- Mazzucato, M (2011) *The Entrepreneurial State*. London: Demos. http://www.demos.co.uk/files/Entrepreneurial_State_-_web.pdf

- Mitchell, P. and Doherty, M. (2015) *Job creation in the circular economy – increasing resource efficiency in Northern Ireland*. ReNEW Report into the Circular Economy in Northern Ireland. <http://www.wrap.org.uk/sites/files/wrap/ReNEW%20CE%20Employment%20Report.pdf>
- Mittra, J., Mastroeni, M. and Tait, J. (2014) *Engaging with Uncertainty and Risk in Agricultural Biotechnology Regulation: Delivering Safety and Innovation*. Report from ESRC Knowledge Exchange Project with Syngenta, Jan. 2014. <http://innogen.ac.uk/reports/883>
- von Moltke, K. (1987) *The Vorsorgeprinzip in West German Environmental Policy*. London: Institute for European Environmental Policy.
- Natural Scotland (2016) *Making things last: a circular economy strategy for Scotland*. Scottish Government, Feb. 2016. <http://www.gov.scot/Resource/0049/00494471.pdf>
- Nowotny, H. (2015) *The Cunning of Uncertainty*. Cambridge, UK; Polity Press.
- OECD (2015) *The Innovation Imperative: Contributing to Productivity, Growth and Well-Being*, OECD Publishing, Paris. DOI: <http://dx.doi.org/10.1787/9789264239814-en>
- OECD (2009) *The Bioeconomy to 2030: designing a policy agenda*. International futures Programme. Paris: OECD. <http://dx.doi.org/10.1787/9789264056886-9-en>
- Omidvar, O., de Grijs, M., Castle, D., Mittra, J., Rosiello, A. and Tait, J. (2014) *Regenerative Medicine: Business Models, Venture Capital and the Funding Gap*. Report to ESRC and InnovateUK, 30th Oct, 2014. <http://www.innogen.ac.uk/downloads/RegenerativeMedicine-BusinessModels-VentureCapital-and-theFundingGap-Oct14.pdf>
- Oye, K. *et al.* (2014) Regulating gene drives: regulatory gaps must be filled before gene drives could be used in the wild. *Science*, 345, 626 – 628.
- Peplow, M. (2016) Synthetic malaria drug meets market resistance. *Nature*, 530, 389-390.
- Pielke R.A. (2007) *The Honest Broker: Making Sense of Science in Policy and Politics*. Cambridge, UK: Cambridge University Press
- Postnote (2015) *Regulation of synthetic biology*. Parliamentary Office of Science and Technology: Postnote No 497, May 2015.
- Presidential Commission for the Study of Bioethical Issues (2010) *New Directions: the ethics of synthetic biology and emerging technologies*. http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf
- Raybould, A. and Poppy, G. (2012) Commercialising GM crops under EU regulations: objectives and barriers. *GM Crops Food*, Jan-Mar, 3(1), 9-20.
- Redford, K.H., Adams, W. and Mace, G.M. (2013) Synthetic Biology and Conservation of Nature: Wicked Problems and Wicked Solutions. *PLoS Biol* 11(4): e1001530. doi:10.1371/journal.pbio.1001530
- Rifkin, J. (1998) *The Biotech Century: Harnessing the Gene and Remaking the World*. *New York Times*. <http://www.nytimes.com/books/first/r/rifkin-biotech.html>
- Royal Commission on Environmental (1989) *Thirteenth Report: the Release of Genetically Engineered Organisms into the Environment*. London: HMSO, Cmd. 720, 1989.
- RSE (2015) *The opportunities from GM and biotechnology for Scotland*. RSE Advice Paper 15-20. (https://www.royalsoced.org.uk/cms/files/advice-papers/2015/AP15_20.pdf)

- SBLC (2016) *Biodesign for the Bioeconomy: UK synthetic biology strategic plan, 2016*.
<https://connect.innovateuk.org/documents/2826135/31405930/BioDesign+for+the+Bioeconomy+2016+-+DIGITAL.pdf/0a4feff9-c359-40a2-bc93-b653c21c1586>
- Sciencewise (2013) *Public views on synthetic biology*. [<http://www.sciencewise-erc.org.uk/cms/public-views-on-synthetic-biology>]
- Sciencewise (2015) *Public attitudes to industrial biotechnology: a review of information on the views and values of the public on industrial biotechnology*. Social Intelligence Report. Department of Business Innovation and Skills: Sciencewise. [<http://www.sciencewise-erc.org.uk/cms/public-attitudes-to-industrial-biotechnology>]
- Seralini, G-E, *et al.*, (2012) Long term toxicity of a Roundup herbicide and a Roundup tolerant genetically modified maize. *Food Chem. Toxicol.* 50, 4221-4231. Retracted by the journal, Jan. 2014. [<http://www.sciencedirect.com/science/article/pii/S0278691513008090>]
- Steedman, S. (2013) *Standards and synthetic biology: structuring knowledge to accelerate innovation*. EU Workshop in Synthetic Biology, 11 Oct., 2013.
<https://connect.innovateuk.org/documents/2826135/9165366/7+Scott+Steedman.pdf/763762eb-c49d-4436-8b28-69bdd03637e9;jsessionid=2B0AC4A4659678575BB695F6A164EB3F.2>
- Stirling, A. (2014) Making choices in the face of uncertainty: strengthening innovation democracy. In *Annual Report of the Government Chief Scientific Adviser, 2014. Innovation: Managing Risk not Avoiding It*. Evidence and Case Studies, pp 49-62.
<https://www.gov.uk/government/publications/innovation-managing-risk-not-avoiding-it>
- Sunstein, C.R. (2005) *The Laws of Fear: Beyond the Precautionary Principle*. Cambridge: Cambridge University Press.
- Sunstein, C.R. (2009) *Going to Extremes: How Like Minds Unite and Divide*. Oxford: Oxford University Press.
- Tait, J. and Banda, G. (2016a) *Proportionate and adaptive governance of innovative technologies: the role of regulations, guidelines and standards (Summary Report)*. Report to the British Standards Institution [<http://www.innogen.ac.uk/downloads/Summary-Report---Adaptive-governance---PRINT.pdf>].
- Tait, J. and Banda, G. (2016b) *Proportionate and adaptive governance of innovative technologies: the role of regulations, guidelines and standards (Full Report)*. Report to the British Standards Institution
http://www.innogen.ac.uk/downloads/Innogen_Institute_BSI_Standards_Project_Main_Report.pdf.
- Tait, J., (2014) Bringing it all Together. In *Annual Report of the Government Chief Scientific Adviser, 2014. Innovation: Managing Risk not Avoiding It*. Evidence and Case Studies, pp 129-136.
<https://www.gov.uk/government/publications/innovation-managing-risk-not-avoiding-it>
- Tait, J. and Barker, G., (2011) Global food security and the governance of modern biotechnologies: opportunities and challenges for Europe *EMBO Reports*, 12, pp763-768.
<http://www.nature.com/embor/journal/v12/n8/pdf/embor2011135a.pdf>
- Tait, J. (2009a) Upstream Engagement and the Governance of Science: the shadow of the GM crops experience in Europe. *EMBO Reports*. Vol 10, Special Issue, pp 18-22.
<http://www.nature.com/embor/journal/v10/n1s/pdf/embor2009138.pdf>

- Tait, J. (2009b) Governing Synthetic Biology: Processes and Outcomes. In eds. Markus Schmidt, Alexander Kelle, Agomoni Ganguli-Mitra and Huib de Vriend, *Synthetic Biology: the Technoscience and its Consequences*. Dordrecht NL: Springer, pp 141-154.
- Tait, J. (2009c) Risk Governance of Genetically Modified Crops in Europe. In International Risk Governance Council (IRGC) Report, *Risk Governance Deficits: an analysis and illustration of the most common deficits in risk governance*. Geneva: IRGC www.irgc.org.
- Tait, J. (2008). Risk Governance of Genetically Modified Crops: European and American Perspectives. In eds. O. Renn and K. Walker, *Global Risk Governance: Concept and Practice Using the IRGC Framework*. Dordrecht, NL: Springer Science and Business Media; pp 133-153.
- Tait, J. with Wield, D., Chataway, J. and Bruce. A. (2007) *Health Biotechnology to 2030*. Report to OECD International Futures Project, "The Bioeconomy to 2030: Designing a Policy Agenda", OECD, Paris, pp 51; <http://www.innogen.ac.uk/reports/487>.
- Tait, J. and Chataway, J. (2007) The governance of corporations, technological change and risk: examining industrial perspectives on the development of genetically modified crops. *Environment and Planning C: Government and Policy*, 25, 21-37.
- Tait, J. (2007) Systemic Interactions in Life Science Innovation. *Technology Analysis and Strategic Management*, 19(3), 257-277, May 2007.
- Tait, J. (2001) More Faust than Frankenstein: the European Debate about Risk Regulation for Genetically Modified Crops. *Journal of Risk Research*, 4(2), 175-189.
- Tait, J. and Levidow, L. (1992) Proactive and Reactive Approaches to Risk Regulation: the Case of Biotechnology, *Futures*, April, 1992, pp 219-231.
- Tait, J. (1988) NIMBY and NIABY: Public Perception of Biotechnology. *International Industrial Biotechnology* 8(6), 5-9.
- UK Synthetic Biology Roadmap Coordination Group (2012) *A Synthetic Biology Roadmap for the UK*. London: Technology Strategy Board. (<http://www.rcuk.ac.uk/RCUK-prod/assets/documents/publications/SyntheticBiologyRoadmap.pdf>)
- US National Research Council (2015) *Industrialisation of Biology: a roadmap to accelerate the advanced manufacturing of chemicals*. Washington DC: National Academies Press. <http://www.nap.edu/catalog/19001/industrialization-of-biology-a-roadmap-to-accelerate-the-advanced-manufacturing>.
- Wackernagel, M. and Rees, W. (1996) *Our ecological footprint: reducing human impact on the earth*. Gabriola Island, BC: New Society Publishers.
- Westra, J. et al., (2016) *Gene drives: policy report*. RIVM Letter, Report 2016-0023. [http://www.rivm.nl/dsresource?objectid=rivmp:304500&type=org&disposition=inline&ns_nc=1]
- Whitty, C.J.M. et al. (2013) Africa and Asia need a rational debate on GM crops. *Nature*, 497, 31-33.